CIGARETTE SMOKING AND
CARBON MONOXIDE

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# CIGARETTE SMOKING AND CARBON MONOXIDE

Prepared for the Council for Tobacco Research

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CONTENTS

## IV B. Chronic Respiratory Effects in Humans

The medical examination of traffic officers stationed at the Holland Tunnell in New York has provided an opportunity to determine the effects of chronic exposure to 70 ppm carbon monoxide. Sievers et al. (1942) examined 156 such officers and failed to find any evidence of injury to health that was attributable to carbon monoxide exposure. There were no signs or symptoms of respiratory abnormalities. Other reports of elevated carbon monoxide levels in highway tunnels have appeared, but the clinical examination of the traffic officers has not been included (Braja and Trompeo, 1964; D'Arca et al. 1964; Miranda et al., 1967; Yamate and Matsumura, 1968).

Astrup et al. (1968) and Klausen et al. (1968) exposed 8 male subjects to inhalation of 0.5% carboxyhemoglobin, resulting in a blood level of 10%. There were no changes in ventilation, circulation or metabolism.

## SUMMARY

I. Introductory remarks. The literature on carbon monoxide has been reviewed to determine its role in cigarette smoking. A total of 3,500 articles dealing with carbon monoxide were examined, half of them appearing between 1966 and 1972, and bibliographies of these are appended to this report. The present status of the interrelationships between cigarette smoking and carbon monoxide is summarized in the following paragraphs by listing a number of generalizations that are grouped into 3 categories: statements that are generally agreed upon or accepted, those that are unsettled or controversial, and those on which no information is available.

II. Carboxyhemoglobin blood levels and cigarette smoking. There is general agreement that cigarette smoke contains carbon monoxide and that a detectable amount of carboxyhemoglobin is present in the blood of habitual smokers. However, the amount of the carboxyhemoglobin content is unsettled and misquoted. The overall mean level for 30 investigations comprising 2,054 subjects is 3.76% saturation in the blood collected 4 to 12 hours after the last cigarette. In 21 of these investigations nonsmokers were compared with habitual smokers; the net difference was a mean of + 2.19%, indicating that the blood of habitual smokers contained this amount more than that of nonsmokers. Immediately after smoking one or more cigarettes, the mean peak level is 5.26%. The phenomenon of "passive smoking" has been examined. The highest level reported for passive smokers was 3.3% for nonsmokers in a room (170 cu m) with a carbon monoxide concentration of

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30 ppm from the consumption of 9.5 cigarettes for each of 11 smokers during a period of 2 hours.

There is no information on the carboxyhemoglobin that smokers sustain throughout a 24-hour period. The level before smoking and the peak level after smoking give the range, but what is needed is an integrated level for the 24-hour period.

III. Sources of carbon monoxide. There is agreement that the blood of nonsmokers contains carboxyhemoglobin derived from endogenous and exogenous sources. The latter include vehicular exhaust, which is a major source of carbon monoxide. Of the 26 investigations of blood levels in nonsmokers, the overall mean for 1,662 subjects was 1.45% carboxyhemoglobin and this may increase two- or fourfold, depending on the level of air pollution. The combination of exposure to vehicular traffic and tobacco smoking causes a further elevation of carboxyhemoglobin approximately equal to the sum of exposure to each. The peak blood levels for 446 subjects had an overall mean of 6.8%. The consequence of this combined exposure to carbon monoxide is unsettled. The effect on the subjects may also be the outcome of exposure to lead, ozone, hydrocarbons and nitrogen oxides from vehicular exhaust.

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IV. Respiratory system. There is general agreement that acute exposure to carbon monoxide producing a blood level of up to 10% carboxyhemoglobin does not influence respiratory minute volume, diffusing capacity or mechanical properties of the lung in healthy subjects. Chronic exposure of tunnel traffic officers to 70 ppm for several years does not influence respiration. The controversial areas are as follows: The

effect of cigarette smoking on patients with chronic lung disease includes an elevated carboxyhemoglobin level and reduction in pulmonary diffusing capacity. That carbon monoxide per se causes disturbance of lung function has not been proven in animals. Exposure of dogs to a mixture of 8 to 14% carbon monoxide in air did not produce ultrastructural changes, but exposure of rats produced swelling of alveolar epithelial mitochondria and nucleoplasm. There is no information on ultrastructural changes in primates which will help resolve differences in species.

V. Circulatory system. It is generally agreed that acute carbon monoxide poisoning produces abnormalities in the electrocardiogram and myocardial lesions. Acute exposure to carbon monoxide, resulting in 10% carboxyhemoglobin saturation, does not influence heart or cardiac output. There are several unsettled claims. That the carbon monoxide content of cigarette smoke causes coronary heart disease has not been proven in animals. On the contrary, exposure of dogs to 100 ppm carbon monoxide for 14 weeks did not produce any exaggeration of the myocardial infarction that was experimentally induced by coronary embolization. A retrospective study of patients in Los Angeles did not show a relationship between carbon monoxide levels and the occurrence of acute myocardial infarction. There is no information on the role of carbon monoxide contained in cigarette smoke in provoking an anginal attack. The investigation comparing cigarette smoking with exposure to vehicular traffic included several constituents. A more direct approach is to compare cigarette smoking with inhalation of carbon monoxide to obtain equivalent levels of carboxyhemoglobin

in the same subject. The increase in capillary permeability induced in human subjects exposed to carbon monoxide alone needs to be compared with exposure to cigarette smoking.

The development of arteriosclerosis by carbon monoxide is another controversial area. The positive evidence is based on animals fed with cholesterol that develop arteriosclerosis following chronic exposure to carbon monoxide. However, examination of individuals who have been exposed to an environment of up to 1,000 ppm with blood levels of 2 to 26% carboxyhemoglobin for an average duration of 10.5 years did not reveal any early onset of arteriosclerosis. One possible explanation of the difference between short-term exposure of animals and long-term exposure of humans is the development of tolerance to carbon monoxide in the latter. No information is available on development of tolerance to carbon monoxide associated with cigarette smoking.

VI. Nervous system. There is general agreement that acute carbon monoxide poisoning causes lesions of cerebral blood vessels, eye and visual pathways, auditory system and brain. There is also agreement that the following effects appear with carboxyhemoglobin levels of 5 to 10%: impairment of critical flicker fusion frequency and alteration of psychomotor abilities. No information is available as to the effect of inhalation of carbon monoxide at the same carboxyhemoglobin levels as that associated with cigarette smoking.

VII. Other organ systems. There is general agreement that acute carbon monoxide poisoning causes disturbance of renal function, the endocrine system and the musculo-skeletal-dermal system. In pregnancy, carbon monoxide is

# I. INTRODUCTORY REMARKS

In recent years there has been increasing concern as to the harmful effects of carbon monoxide released as an air pollutant. The importance of cigarette smoking as a source of carbon monoxide has been recently stressed. This review is an attempt to clarify the role of carbon monoxide in cigarette smoking. The relationship will be analyzed in terms of carboxyhemoglobin blood levels and their influence on the respiratory, circulatory, nervous, renal, reproductive, endocrine and musculoskeletal systems.

At the outset it is pertinent to summarize the present state of knowledge relating to carbon monoxide in general and to carbon monoxide in cigarette smoke in particular. The information is summarized in the following publications:

a. The toxicity of carbon monoxide has been reviewed by Sayers and Davenport (1930), Killick (1940), Lilienthal (1950), Root (1962) and Theodore et al. (1971). These review articles have appeared at intervals of a decade and do not include the cigarette smoke as a source of carbon monoxide.

b. The importance of carbon monoxide as an air pollutant has been reviewed by Goldsmith (1964), Kaye (1965), Finck (1966), Giever (1967), Goldsmith and Landaw (1968), Beard (1969), Leclerq and Proteau (1970), Casarett (1971) and Jech (1972). These reviews appearing at yearly intervals emphasize the origin of carbon monoxide poisoning from sources other than cigarette smoking.

c. A symposium entitled "Biological Effects of Carbon Monoxide," edited by R. F. Coburn, appeared in 1970. Most investigators active in carbon monoxide research participated in this meeting. There is one article relating to cigarette smoking as a source of carbon monoxide (Lawther and Cummins, 1970).

d. Government agencies have released three documents concerning regulation of carbon monoxide levels. The National Academy of Science and the National Academy of Engineering have jointly released "Effects of Chronic Exposure to Low Levels of Carbon Monoxide on Human Health, Behavior, and Performance" in 1969; the Environmental Health Service has released "Air Quality Criteria for Carbon Monoxide" in 1970; and the National Institute for Occupational Safety and Health has published "Criteria for a Recommended Standard: Occupational Exposure to Carbon Monoxide" in 1972. The major change was the reduction in the threshold limit value from 100 ppm for carbon monoxide to 50 ppm. The following authors have written review articles on regulation of control of carbon monoxide levels: Dinman (1968); Goldsmith and Cohen (1969), DuBois (1970), Grut et al. (1970) and Rossin and Roberts (1972).

e. The carbon monoxide liberated during the use of tobacco is reviewed in the following monographs: "Tobacco: Experimental and Clinical Studies," by Larson et al. (1961), and supplements by Larson and Silvette (1968, 1971); "Tobacco and Tobacco Smoke," by Wynder and Hoffmann (1967); and "Nikotin: Pharmacologie und Toxikologie des Tabakrauches," edited by Schievelbein

(1968). In the publications prepared by the National Clearinghouse for Smoking and Health, there has been an increasing amount of space devoted to carbon monoxide ("Smoking and Health," 1964; "The Health Consequences of Smoking," 1967, 1968, 1969, 1971 and 1972). In the 1972 supplement, the danger to the nonsmoker who inhales the carbon monoxide of the smoke liberated by a smoker has been emphasized. The contents of these publications relating to carbon monoxide in cigarette smoke are discussed in section IX below.

f. The bibliography of carbon monoxide was compiled in 1966 by Cooper. Among the 983 articles abstracted, 22 were devoted to carbon monoxide in smoking.

The present review is written primarily to discuss the relationship between cigarette smoking and carbon monoxide. Articles which directly relate to carbon monoxide and cigarette smoking are reviewed in this document. The investigations dealing with objective measurements of carbon monoxide exposure are emphasized, particularly those which relate to the effects of cigarette smoking on body systems (sections II to VIII). The articles which discuss the significance of carbon monoxide in cigarette smoking have been scrutinized for validity of statements. Included in this commentary (section IX) are the statements which appeared in all the volumes of "Smoking and Health" (1967 to 1972). The bibliography for 1966 to 1972 on carbon monoxide in general is appended to complete the reference list started by Cooper for articles appearing up to 1966 (section XI).

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## II. CARBOXYHEMOGLOBIN BLOOD LEVELS AND CIGARETTE SMOKING

The most important single measurement for assessing the amount of exposure to carbon monoxide is the blood level of carboxyhemoglobin. The portion of hemoglobin present in the form of carboxyhemoglobin cannot combine with oxygen and therefore cannot carry oxygen from the lungs to the tissues. The techniques for measuring carboxyhemoglobin are discussed in the articles under additional bibliography list no. 1. The nature of the binding between carbon monoxide and hemoglobin resulting in a shift of the oxyhemoglobin dissociation curve to the left is covered by additional bibliography list no. 2. The release of hemoglobin from carboxyhemoglobin during the elimination of carbon monoxide and its oxidation by living tissues are covered by the publications in additional bibliography list no. 3. The accumulation of carbon monoxide in enclosed spaces, such as an aircraft, submarine or tunnel, is covered by additional bibliography list no. 4. This section will discuss the details of the investigation that relate directly to cigarette smoking and its consequences on the level of carboxyhemoglobin in the blood.

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### A. Habitual Smokers

The first identification of carboxyhemoglobin in blood of smokers was accomplished by Hartridge (1919-1920). He estimated the level in one smoker to be 6% and in another to be absent. A more extensive investigation was completed byGettler and Mattice (1933), who compared 4 groups of habitual cigarette smokers. The group of 12 rural dwellers had a mean value

of 1.2% carboxyhemoglobin in the blood, while 18 New York City residents had a mean of 1.4%, 12 New York City cleaners a mean of 3.5%, and 2 New York City taxi drivers a mean of 13.5%. These results proved for the first time that the carboxyhemoglobin contained in blood of habitual smokers was not only the result of cigarette smoking but was also the outcome of inhaling an atmosphere containing carbon monoxide released from automobile exhaust and other sources.

There have been 28 additional reports of carboxyhemoglobin in blood levels among cigarette smokers and the results are summarized in Table 1. The mean values do not represent the effect of cigarette smoking because the contribution of carbon monoxide in the atmosphere has to be subtracted. The last column in Table 1 is the net level of carboxyhemoglobin which can be attributed to cigarette smoking and was obtained by subtracting the mean blood levels for controls who were nonsmokers. The following generalizations can be made from the published results.

1. The 30 investigations summarized in Table 1 were performed in various cities in the United States and Europe. The highest mean level is 16.2% for a group of 6 U. S. Army enlisted men (Meigs, 1948). This represents an error in the analysis, since the blood levels for nonsmokers were also high. All the other mean levels were below 10% carboxyhemoglobin.

2. The overall mean level for 2,054 subjects reported in the 30 investigations is 3.76%. This represents the average blood level for smokers in the morning, 4 to 12 hours after they smoked a cigarette.



3. The contribution of atmospheric pollution to the increased blood levels of carboxyhemoglobin can be derived by subtracting the blood levels for controls

who were nonsmokers. Twenty-one of the investigations included nonsmokers, so that it was possible to subtract their mean levels from those of habitual smokers. The net difference between 2 groups represents the contribution from smoking alone, which amounted to a mean of +2.19% of carboxyhemoglobin for 2,781 subjects. This mean value was calculated regardless of the number of cigarettes consumed.

4. Ten investigators related the amount of cigarettes consumed daily to blood levels of carboxyhemoglobin. The consumption of 20 or less cigarettes per day showed the following net change in blood carboxyhemoglobin levels in each case: +1.6% (Schmidt, 1939); +2.4% (Schrenk, 1942); +2.1% (Parmeggiani and Gilardi, 1952); +1.0% (Goldsmith et al, 1963); +1.9% (Curphey et al, 1965); +0.3% (Balbo et al, 1966); and +0.9% (Rouch et al, 1971). The net changes in blood carboxyhemoglobin levels for subjects consuming one or more cigarettes were respectively: +2.9% (Schmidt, 1939); +3.7% (Schrenk, 1942); +3.5% (Parmeggiani and Gilardi, 1952); +1.1% (Goldsmith et al, 1963); +3.6% (Curphey et al, 1965); +2.0% (Balbo et al, 1966); and +8.0 (Yacoub et al, 1970). The last-mentioned value represents the highest net level of carboxyhemoglobin, next to the +11.0% referred to above as reported for the U. S. Army enlisted men.

(Table 1 appears on the next page.)

Table 1 Carboxyhemoglobin levels in the blood of habitual smokers.[1]

| Reference (Year) | Nature of habitual smokers (Cigarette consumption) | No. of Subjects | Carboxyhemoglobin blood level % Smokers Mean ± SD | (Range) | Non-smokers[2] Mean | Net Δ |
|---|---|---|---|---|---|---|
| Hartridge (1919-1920) | London volunteers | 2 | 3.0 | (0-6) | | |
| Gettler and Mattice (1933) | New York residents | 18 | 1.4 | (1.0-4.1) | | |
| | New York street cleaners | 12 | 3.5 | (1.2-0.9) | | |
| | New York taxi drivers | 2 | 13.5 | (8.0-19) | | |
| | Rural dwellers | 12 | 1.2 | (0.5-3.6) | | |
| Ruhl and Lin (1936) | Berlin volunteers | | | | | |
| | (non-inhalers in morning) | 21 | 0.6 | | | |
| | (inhalers in morning) | 25 | 0.5 | | | |
| | (heavy inhalers in morning) | 13 | 1.3 | | | |
| | (heavy inhalers in evening) | 13 | 2.6 | | | |
| Schmidt (1939; 1940) | Bonn volunteers | | | | | |
| | (20-30/day) | 3 | 3.5 | | 0.6 | +2.9 |
| | (> 30/day) | | 7.2 | | | +6.6 |
| | (10-20/day) | | 2.2 | | | +1.6 |
| | (< 10/day) | | 1.5 | | | +0.9 |
| Schrenk (1942); Sievers, Edwards Murray and Schrenk (1942) | Holland tunnel workders | | | | | |
| | (<20/day | 39 | 4.1 ± 1.9 | | 1.7 | +2.4 |
| | (>20/day) | 21 | 5.4 ± 1.8 | | | +3.7 |
| | (pipe) | 5 | 2.5 | | | |
| | (cigar) | | 3.2 | | | |
| Wennesland 1945 | Stockholm volunteers | | | | | |
| | (<15/day) | 35 | | (0.5-10.5) | | |
| | (pipe) | 7 | | (0-11.5) | | |
| Meigs 1948 | US army enlisted men | | | | | |
| | (6-20/day | 6 | 16.2 | (1.9-45) | 5.2 | +11.0 |
| Parmeggiani and Gilardi (1952) | Italian volunteers | | | | | |
| | (10-12/day) | 14 | 4.9 | (1-9) | 2.8 | +2.1 |
| | (15-25/day) | 6 | 6.3 | (2-9.5) | | +3.5 |
| | (30-40/day) | 3 | 9.3 | (6-14) | | +6.5 |
| Barthe, Paris, Duchemin and Thomas (1953) | Paris workers | 100 | | (0.8-2.0) | | |
| Ruel and Barthe (1954) | Paris workers | | | | | |
| | (<10/day) | | 1.0 | | | |
| | (10 -15/day) | | 1.7 | | | |
| | (>20/day ) | | 2.7 | | | |
| Valic and Duric (1954) | Yugoslavian workers | 75 | 3.8 ± 1.9 | | 0.9 | +2.9 |
| Gaensler, Cadigan, Ellicott, Jones and Marks (1957) | Boston workers | 9 | 4.7 | (3.1-7.9) | 0.9 | +3.8 |
| Dahlström, Nordström-Öhrberg and Rothschild (1958) | Stockholm volunteers | 6 | 2.1 | (1.2-3.0) | 0.7 | +1.4 |

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Table 1 (continued)



| Reference (Year) | Nature of habitual smokers (Cigarette consumption) | No. of Subjects | Carboxyhemoglobin blood level % Smokers Mean ± SD | (Range) | Non-smokers[2] Mean | Net |
|---|---|---|---|---|---|---|
| rinder and Harper (1962) | Sunderland volunteers | 3 | 3.8 | (3.2-4.8) | 0.9 | +2.9 |
| Hofreuter, Catcott and Xintaras (1962) | Cincinnati volunteers | 19 | 2.9 | | 1.9 | +1.0 |
| Goldsmith, Schuette and Novick (1963) | San Francisco longshoremen | | | | | |
| | (<10/day) | 429 | 2.3 | | 1.3 | +1.0 |
| | (10-40/day) | 1035 | 3.4 | | | +1.1 |
| | (>40/day) | 233 | 5.5 | | | +4.2 |
| Curphrey, Hood and Perkins (1965) | Los Angeles longshoremen | | | | | |
| | (light) | 55 | 2.3 | | 0.4 | +1.9 |
| | (medium) | 153 | 3.0 | | | +2.6 |
| | (heavy) | 29 | 4.0 | | | +3.6 |
| Ayres, Gianelli and Armstrong (1965) | New York volunteers | 25 | 4.2 | | 0.9 | +3.3 |
| Balbo, Marucci and Ronchi (1966) | Paris workers | | | | | |
| | (5/day) | 34 | 2.1 | (0-9.8) | 1.9 | +0.2 |
| | (10/day) | 32 | 2.2 | (0-9.5) | | +0.3 |
| | (15/day) | 16 | 2.2 | (0-5.9) | | +0.3 |
| | (20/day) | 20 | 2.2 | (0-6.9) | | +0.3 |
| | (30/day) | 7 | 2.8 | (0-5.2) | | +2.0 |
| cIlvaine, Nelson and Bartlett (1969) | Durham workders | 5 | 3.8 | | 1.6 | +2.2 |
| Bhown, Maitrya and Haq (1969) | Indian beedi smokers | | | | | |
| | (<10/day | 7 | 4.8 | (3.4-5.6) | | |
| | (10-19/day) | 8 | 5.9 | (5.6-6.1) | | |
| | (20-29/day) | 8 | 6.9 | (6.6-7.3) | | |
| | (>29/day) | 7 | 9.4 | (8.5-10.5) | | |
| Yacoub, Faure, Mallion and Cau (1970) | Paris workers | | | | | |
| | (20/day inhaled) | 90 | 9.5 | | 1.5 | +8.0 |
| | (20/day non-inhaled) | 97 | 6.0 | | | +4.5 |
| Rouch, Rioufol and Bourbon (1971) | Toulouse volunteers | | | | | |
| | (< 10/day) | 5 | 2.5 | (1.0-5.5 | 1.6 | +0.9 |
| | (> 10/day) | 15 | 4.25 | (1.0-11.0) | | +2.6 |
| Brewer, Eaton, Weil and Grover (1970); Brewer, Eaton, Grover and Weil (1971) | Leadville volunteers | 20 | 6.6 ± 2.7 | | | |
| Weiss, Slawsky and Desforges (1971) | Boston patients with fibrosis | 8 | 4.2 ± 2.7 | | 1.5 | +4.2 |
| tley (1971) | Los Angeles residents | 81 | 5.7 | (3.2-14.2) | 1.5 | +4.2 |
| Hansen, Wilke, Malorny and Gothert (1972) | Hamburg workers | 40 | 4.9 ± 1.0 | | 0.75 | +4.2 |

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| Reference (Year) | Nature of habitual smokers Cigarette consumption) | No. of Subjects | Carboxyhemoglobin blood level % | | | |
|---|---|---|---|---|---|---|
| | | | Smokers Mean ± SD (Range) | | Non-smokers Mean | Net Δ |
| -turson, Garby, Robert and Zaar (1972) | Uppsala volunteers | 6 | 2.7 | (1.5-4.4) | 1.27 | +1.4 |
| Mean (overall for number of subjects) | | | 3.76 (2954 subjects) | | | +2.19 (2781 subject |

1 Some of the values were reported in volumes % and are expressed in this table as saturation % assuming normal hemoglobin values.

2 See Table 4 for details.

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> One of the toxic products of the automobile is carbon monoxide. Exposure for 1 hour to a concentration of this gas of 120 parts per million causes inactivation of about 5 percent of the body's hemoglobin and commonly leads to dizziness, headache, and lassitude. Concentrations of carbon monoxide as high as 100 ppm often occur in garages, in tunnels, and behind automobiles. Such concentrations are tiny in comparison with those (42,000 ppm) found in cigarette smoke. The smoker survives because most of the time he breathes air not so heavily polluted. However, in a poorly ventilated, smoke-filled room, concentrations of carbon monoxide can easily reach several hundred parts per million, thus exposing smokers and nonsmokers present to a toxic hazard.

In this article, the comparison of concentration of carbon monoxide is as follows: 100 ppm for garages and tunnels and 42,000 ppm in cigarette smoke. The latter represents 4.2 carbon monoxide in pure cigarette smoke. This concentration is not inhaled continuously, but is diluted by air in the lungs at the time of inhalation of cigarette smoke. After exhalation, atmospheric air enters to replace the cigarette smoke. Ringold et al. (1962) analyzed the expired air to determine the integrated concentration of carbon monoxide therein: that of heavy smokers had a concentration of 16.4 ppm, light smokers 7.7 ppm, and non-smokers 0.08 ppm (see page 19).

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## II B. Influence of Smoking on Alveolar Air and Blood Levels of Carboxyhemoglobin

Jongbloed (1939) analyzed the carbon-monoxide content in alveolar air. A trace of carbon monoxide (about 0.0001% or 4 ppm) was detectable in the alveolar air of nonsmokers. In one smoker the content was 10 ppm in the morning before smoking. Then the subject was given 4 cigarettes, each one taking 12 min to smoke with an intervening 12-minute rest period. The results were as follows:

| | |
|---|---|
| before 1st cigarette | 14.0 ppm |
| after " " | 17.9 " |
| before 2nd " | 19.4 " |
| after " " | 23.2 " |
| after 3rd " | 27.1 " |
| after 4th " | 31.5 " |
| 32 min after 4th cigarette | 29.0 " |
| 52 min " " " | 26.6 " |
| 72 min " " " | 23.7 " |

There was a progressive increase in the level of carbon monoxide in the alveolar air up to the end of smoking the 4th cigarette. Then a fall occurred in the concentration of carbon monoxide in the alveolar air.

Other investigators have confirmed the observation of Jongbloed. Ringold et al. (1962) analyzed the expired air after a 20-second breath-holding period. The mean ± SD levels of carbon monoxide were as follows:

| | |
|---|---|
| Nonsmokers (93 subjects) | 0.8 ± 4.7 ppm |
| Heavy smokers (41 subjects) | 16.4 ± 12.6 " |
| Light smokers (25 subjects) | 7.7 ± 10.9 " |
| Pipe or cigar (9 subjects) | 3.8 ± 4.9 " |

Cohen et al. (1971) reported similar observations and correlated expired air levels of carbon monoxide with blood levels of carboxyhemoglobin.

The results of investigations relating to blood carboxyhemoglobin

levels are summarized in Table 2. The essential features of the table are:

1. The 11 investigations consisting of measurements of carboxyhemoglobin in blood, resulted in a mean peak level of 5.26% in 29 pooled subjects. The net effect of smoking which was calculated in 15 subjects was an increase of 3.81% of carboxyhemoglobin.

2. There are isolated values as high as 12.3% (Earach et al, 1941), 10% (Ruhl and Lin, 1936) and 6.5% (Whitehead and Worthington, 1961). However, since the control value prior to smoking was not measured, it was not possible to calculate the net effect of smoking.

3. None of the investigations summarized in Table 2 determined the duration of the rise in carboxyhemoglobin. On the basis of work concerning experimental inhalation of carbon monoxide mixture, the duration depends on the concentration of inspired air. There is probably a slow fall in carboxyhemoglobin until the next cigarette is smoked.

After cessation of smoking, a reduction occurs in blood levels of carboxyhemoglobin (Belli and Guiliani, 1955; Ramsey, 1972; Rosenberg, 1968, 1971, 1972). The rate of fall in concentration was accelerated by exercise or muscular effort ("Castellino, 1955; Crosetti et al, 1966; Shields, 1971). **1005051083**

Animals have been exposed to cigarette smoke for the investigation of its effect. The blood level of carboxyhemoglobin is elevated in mice (Leuchtenberger et al, 1965), hamsters (Dontenwill et al, 1966, 1967) and rats (Driscoll et al, 1972). In the last-mentioned species, the blood level of carboxyhemoglobin was influenced by the nature of cigarette used. With unfiltered smoke, the rat held its breath, whereas filtered smoke was inhaled with continuation of thoracic respiration.

(Table 2 appears on the next page.)

Table 2. Acute effects of cigarette smoking on carboxyhemoglobin levels.[1]

| Reference (Year) | Number of Cigarettes | No of Subjects | Peak Carboxyhemoglobin blood levels % Mean | (Range) | Δ |
|---|---|---|---|---|---|
| anson and Hastings (1933) | 10-15 | 6 | 4.3 | (3.1-6.7) | |
| Ruhl and Lin (1936) | 1-2 | 5 | | (3.2-10) | |
| Schmidt (1939, 1940) | 1<br>5 | 1<br>2 | | | +1.1<br>+1.6; +4 |
| Hsi-Pu and LiMing (1940) | 1-5 | 43 | (<5 in 80% of subjects) | | |
| Barach, Eckman and Molomut (1941) | 20 | 18 | 5.7 | (2.2-12.3) | |
| MacFarland, Roughton, Halperin and Niven (1944) | 1<br>3 | 1<br>1 | | | +2.0<br>+4.0 |
| Fabre, Truhaut and Berrod (1951) | 24 | 5 | 4.85 | | +2.7 |
| Parmeggiani and Gilardi (1952) | 2 | 1 | | | +3 |
| Goldsmith, Terzaghi and Hackney (1963) | 12 | 1 | | | +11.9 |
| Bowden and Woodhall (1964) | 2 | 2 | | | +1.5 |
| Hamill and O'Neill (1969) | 20 (cigars) | 1 | | | +13 |
| Mean (overall for number of subjects) | | 5.26 (29 subjects) | | | +38 (15 subjects) |

[1] Some of the values were reported in volumes % and are expressed in this table as saturation % assuming normal hemoglobin values.

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## II C. Passive Smoking

The phenomenon of "passive smoking" refers to the exposure of nonsmokers in an enclosed space containing smoke generated by cigarette smoking. The consequence to the individual in such a situation was first described by Jones et al. (1923), who studied the occupants of a non-ventilated room of approximately 1,000 cu ft capacity, filled with smoke liberated from cigars, cigarettes, stogies or pipe tobacco. The highest concentration of carbon monoxide was 200 ppm and the highest concentration of carboxyhemoglobin in the blood was 5%. Within 15 min, the occupant became uncomfortable and in 45 to 60 min it was necessary for him to wear goggles to prevent eye irritation.

Yaglou (1955) determined the rate of ventilation for a room of 1,410 cu ft, which contained 3 to 4 smokers consuming 24 cigarettes per hr. The passive smokers suffered from headache, watering of the eyes, irritation of the nose and throat, a feeling of depression, and loss of concentration power for reading, when the ventilation was less than 15 cfm per smoker. A ventilation of 25 cfm per smoker was considered as acceptable in preventing these complaints. There were no analyses of blood reported for the subjects.



The consequences of passive smoking have been quantitatively measured by Oettel (1967), Markiewicz (1970) and Harke (1970). All three investigators measured the amount of nicotine absorbed by the passive smoker. Only Harke (1970) determined carboxyhemoglobin levels in the blood of active and passive smokers. In a non-ventilated room, 57 cubic meters in size, filled with smoke liberated from 42 cigarettes for 16 to 18 min, the level would reach as high as

48 ppm. In another room, with a size of 170 cu m, 11 smokers each consumed 9.5 cigarettes within 2 hours. In the presence of a carbon monxoide concentration of 30 ppm, the 11 active smokers had a mean carboxyhemoglobin level of 7.5 ± 0.8% in the blood, while the 7 passive smokers had a level of 3.3 ± 1.4%. With a room concentration of 5 ppm, the respective levels were 5.8 ± 1.6% and 3.3 ± 1.4%; with concentrations of $<$ 5 ppm, the blood levels were respectively 5.0 ± 1.8% and 2.7 ± 1.2%. The effect of exposing the passive smokers to from 5 to 30 ppm caused a net increase of 0.5% in carboxyhemoglobin.

From the above results, Harke (1970) concluded that it is unlikely to find nonsmokers in a room absorbing a significant amount of cigarette smoke. The criticisms by Hess (1971), Schmidt (1971) and Portheine (1971) were largely directed against the measurement of nicotine absorption. The comments regarding carbon monoxide were answered in a rebuttal by Harke (1971), so that the carboxyhemoglobin levels remain valid.

The "passive smoking" situation has been determined by measurement of carbon monoxide in the air. Dublin (1972) reported a concentration of 20.5 to 32.5 ppm in a position next to the smoker in a room ventilated 12.5 times per hour. At the far end of the room the concentration was 13 to 17 ppm. Passive smoking has also been investigated in rats, mice and hamsters (Reckzeh et al, 1969). In these studies, nicotine was also absorbed by the passive smoker.

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## II. D. Carbon Monoxide Content of Cigarette Smoke

The presence of carbon monoxide in cigarette smoke and its absorption by the blood were recognized as early as 1899 by Wahl. By shaking a few drops of blood in 2 or 3 mouthfuls of tobacco smoke, he studied the uptake of carbon monoxide from tobacco smoke by the blood of smokers. The presence of carbon monoxide was confirmed by spectroscopy. Wahl concluded that the quantity taken up was insufficient to produce any ill effects. A similar conclusion was arrived at by Lehmann (1908), Culverwell (1915) and Dixon (1927 a and b).

A more direct approach has been to measure the amount of carbon monoxide liberated from cigarette smoke. One gram of tobacco yields a variable amount of carbon monoxide, depending on the method of obtaining the tobacco smoke, the rate of smoking, the closeness of pack and the nature of use, i.e., by cigarette, pipe or cigar. Table 3 summarizes the results of 10 investigations of the amount of carbon monoxide emanating from cigarettes. The mean values range from less than 1 ml to 62 ml of carbon monoxide per gram of tobacco. A convenient median level is 25 ml, which would mean that a cigarette weighing about 1 g, burning in a space of 1 cu m, would result in a concentration of 25 ppm carbon monoxide. In a larger space of 100 cu m, it would require 100 cigarettes to approach a concentration of 25 ppm, or 200 cigarettes one of 50 ppm, assuming that there is no ventilation and that no carbon monoxide is absorbed by the smokers or by the objects inside the room. This calcuation, based on the amount of carbon monoxide liberated from a cigarette, makes it unlikely that enough carbon monoxide can be contained in a room to be a hazard to nonsmoking occupants. Bridge and Corn

(1972) have arrived at the same conclusion by monitoring carbon monoxide levels in a chamber containing cigarette smoke generated by a machine.

The concentration of carbon monoxide in the cigarette smoke ranges from 2 to 7% (Table 3). As the cigarette was burned and became shorter, the concentration of carbon monoxide was increased (Jarrell and Burde, 1965; Waltz and Hausermann, 1965; Baxter and Hobbs, 1967; Owen and Reynods, 1967; Krusznynski and Henriksen, 1969).

The amount of carbon monoxide in cigarette smoke that is absorbed in the lung has been calculated in a number of ways. Bokhoven and Niessen (1961) measured the concentration of carbon monoxide in the expired air of the same individual with and without inhaling the cigarette smoke. The difference in carbon monoxide concentration in 3 individuals, expressed as % absorbed, averaged 82%. Haebisch (1970) performed a similar analysis and concluded that approximately 7.5 ml of carbon monoxide is absorbed by smoking 45 mm of a cigarette. Dalhamn et al (1968) performed an analysis of smoke administered with a motorized syringe, which drew a 2-second 35 ml puff of smoke, and analyzed the sample before and after the smoke was exhaled by the subject. In 5 subjects, 54 ± 12.7% was retained after deep inhalation, while only 3 ± 0.7% was absorbed when the smoke was kept in the mouth and prevented from reaching the lungs.

(Table 3 appears on the next page.)

Table 3. Measurement of carbon monoxide liberated from tobacco.

| Reference (Year) | ml carbon monoxide/ g tobacco | % carbon monoxide in smoke |
|---|---|---|
| Toth (1907) | 0.1-0.3 | |
| Marcelet (1907) | 20-80 | |
| Lee 1908 | 4.1 | |
| Lehmann (1909) | 15-23.5 | |
| Armstrong (1922) | 0.89-1.24 | |
| Baumberger (1923) | 8.3 | |
| Ehrismann and Abel (1934) | 17.25-35 | |
| Saruta (1937) | 62.7 | |
| Kohn-Abrest (1949) | 40.0 | |
| Osborne, Adamek and Hobbs (1956) | | 3.3-5.7% |
| Philippe and Hobbs (1956) | | 2.8-5.7% |
| Stenhagen (1959) | (12-53 mg/cigarette) | |
| Mumpower, Lewis and Touey (1962) | | 5.1 % |
| Newsome and Keith (1965) | | 5-11% |
| Keith and Tesh (1965) | | 3.2% |
| Scassellatti Sforzolini and Savino (1968) | | (110 mg/$m^3$) |
| Grob (1968) | | 3.2% |
| Harke and Drews (1968) | | 3.4-7.7% |
| Otsuka, Fujiwara, Ikawa and Hirayama (1970) | | 3.6% |

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## III. SOURCES OF CARBON MONOXIDE

The interpretation of the significance of carboxyhemoglobin levels in the blood included the contribution from exogenous carbon monoxide in the atmosphere, as well as endogenous carbon monoxide that is found in the tissues. The details of the contribution of these forms of carbon monoxide are discussed in the articles in additional bibliography list no. 5, dealing with atmospheric carbon monoxide, and additional bibliography list no. 6 on endogenous carbon monoxide. Pollution of the air by factories and by vehicular exhausts are covered respectively in additional bibliography lists nos. 7 and 8. This section will discuss those articles that include analysis of carboxyhemoglobin in the blood of individuals that have been exposed to the sources of carbon monoxide other than cigarette smoking.

### A. Carboxyhemoglobin Levels in the Blood of Nonsmokers

It was stated in section II-A that the carboxyhemoglobin contained in the blood of habitual smokers included the contribution from exogenous and endogenous sources of carbon monoxide. Table 4 summarizes the results of 26 investigations of blood levels in nonsmokers. The overall mean for 1,662 subjects was 1.45%. The individual averages varied from 0.4 to 5.2. In cities such as London, Los Angeles and Milan, the residents show the following mean levels of carboxyhemoglobin-respectively: 3.5, 2.3 and 2.8. These values represent a significant contribution from carbon monoxide pollution in the atmosphere.

(Table 4 appears on the next page.)

Table 4. Carboxyhemoglobin levels in the blood of nonsmokers.[1]

| Reference (Year) | Nature of nonsmoker | No of Subjects | Carboxyhemoglobin blood levels % Mean ± SD | (Range) |
|---|---|---|---|---|
| nson and Hastings (1953) | Chicago residents | 7 | 1.5 | (1.2-1.9) |
| Schmidt (1939) | Bonn residents | 14 | 0.6 | (0.2-1.1) |
| Meigs (1948) | US army enlisted men | 4 | 5.2 | (0-8.8) |
| Parmeggiani and Gilardi (1952) | Milan residents | 9 | 2.8 | (0-4) |
| Barthe, Paris, Duchemin and Thomas (1953) | Paris residents | 30 | | (0.6-1.2) |
| Ruel and Barthe (1954) | Paris residents | | 0.5 | |
| Valic and Duric (1954) | Yugoslavian residents | 75 | 0.9 ± 0.42 | |
| Gaensler, Cadigan, Ellicott, Jones and Mark (1957) | Boston residents | 9 | 0.9 | (0.6-1.2) |
| Dahlström, Nordström-Öhrberg and Rothschild (1958) | Stockholm residents | 14 | 0.7 | (0.4-0.8) |
| hitehead and Worthington (1961) | Warwick residents | 6 | 0.8 | (0.-1.5) |
| Trinder and Harper (1962) | Sunderland residents (adults) | 23 | 0.9 ± 0.3 | (0.4-2.1) |
| | (children) | 24 | 0.6 ± 0.2 | (0.3-1.0) |
| Hofreuter, Catcott and Xintaras (1962) | Cincinnati residents | 6 | 1.9 | |
| Goldsmith, Schuette and Novick (1963) | San Francisco longshoremen | 764 | 1.3 | |
| Goldsmith, Terzaghi and Hackney (1963) | Los Angeles resident | 1 | 2.3 | |
| Bowden and Woodall (1964) | Halton residents | 42 | 0.7 ± 0.3 | (0.2-1.5) |
| Curphrey, Hood and Perkins (1965) | Los Angeles longshoremen | 115 | 0.4 | |
| Ayres, Giannelli and Armstrong (1965) | New York residents | 28 | 0.9 | (0.1-1.9) |
| lbo, Marucci and Ronchi (1966) | Paris residents | 44 | 1.9 | (0-7) |
| McIlvaine, Nelson and Bartlett (1969) | Durham residents | 10 | 1.6 | |
| Lawther and Commins (1970) | London residents | 165 | 3.5 | |

Table 4. (continued)

| Reference (Year) | Nature of nonsmoker | No of Subjects | Carboxyhemoglobin blood levels % Mean ± SD (Range) | |
|---|---|---|---|---|
| Jacoub, Faure, Mallion and Cau (1970) | Paris residents | 113 | 1.5 | |
| Rouch, Rioufol and Bourbon (1971) | Toulouse residents | 23 | 1.6 | (1.0-3.5 |
| Weiss, Slawsky and Desforges (1971) | Boston residents | 13 | 1.5 ± 0.8 | |
| Motley (1971) | Los Angeles residents | 115 | 1.5 | (0.2-2.9) |
| Hansen, Wilke, Malorny and Gothert (1972) | Hamburg residents | 37 | 0.75 | |
| Arturson, Garby, Robert and Zaar (1972) | Uppsala residents | 11 | 1.3 | (0.9-1.7) |
| Mean (overall for number of subjects) | | | 1.45 (1662 subjects) | |

[1] Some of the values were reported in volumes % and are expressed in this table as saturation % assuming normal hemoglobin values.

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III B. Vehicular Traffic and Smoking

One major source of air pollution in general and of carbon monoxide in particular is automobile exhaust. Blood samples collected from vehicular drivers, traffic policemen, garage operators and miscellaneous workers show an increase in content of carboxyhemoglobin after exposure. The results of 19 investigations summarized in Table 5 indicate an overall average in 84 subjects of an increase of 1.1% of carboxyhemoglobin following 4 to 8 hours of exposure to vehicular traffic. The average peak level for 1,481 subjects was 3.9%.

The combination of exposure to vehicular traffic and cigarette smoking has been investigated by 8 groups and is summarized in Table 6. The peak blood levels showed an overall average of 6.8% of carboxyhemoglobin for 446 subjects. There is an increase of 2.9% in carboxyhemoglobin as a result of smoking and this value is close to the increase of 3.8% reported for subjects not exposed to vehicular traffic (see section IIB).

The most extreme example of combining cigarette smoking and exposure to automobile exhaust was reported by Srch (1967), who placed 4 subjects in an automobile with doors and windows closed inside a closed garage. Two of the subjects were smokers of 20 to 30 cigarettes daily, who were asked to smoke 5 cigarettes. Before smoking, the blood showed 5% of carboxyhemoglobin. After smoking 5 cigarettes, the blood levels had a mean value of 10%. The two nonsmokers in the automobile had 2% of carboxyhemoglobin before and 5% after the test. This situation rarely

occurs in the ordinary course of events.

There is no reason to suspect that the blood levels of carboxyhemoglobin attained by the combination of cigarette smoking and exposure to vehicular traffice are responsible for the occurrence of vehicular accidents and poor driving (Boeck, 1958; Williams, 1964). The mechanical properties of the lung do not show any abnormality attributable to the exposure to cigarette smoking and vehicular traffic (Reichel et al, 1970). The incidence of sick rates among smokers was significantly higher than among nonsmokers who were exposed to carbon monoxide in the atmosphere (Fiandaca and Vercellotti, 1964; Mountain et al, 1968). There is a reduction in reaction time in drivers exposed to 90 minutes of commuting traffic (Ramsey, 1970). In all of these reports, although an elevation of carboxyhemoglobin is mentioned, a cause and effect relationship has not been established. The exposure to vehicular traffic is associated with inhalation of lead, ozone, hydrocarbons and nitrogen oxides, each of which can also contribute to the effect attributed to cabon monoxide alone. Literature on the toxicity of automobile exhaust is listed as additional bibliography No. 8.

Table 6. Carboxyhemoglobin blood levels of smokers following exposure to vehicular traffic.

| Reference (Year) | Nature of subjects | No. of subjects | Carboxyhemoglobin blood levels % Before | After smoking and exposure | | | Net Δ compared |
|---|---|---|---|---|---|---|---|
| | | | Mean | Mean ± SD | (Range) | Δ | Nonsmok |
| DeBruin, Bult and Van Haeringen (1965) | Amsterdam policemen | 14 | 4.6 | 4.9 | | +0.3 | +2.9 |
| Chovin (1967) | Paris policemen | 35 | 3.7 | | | | +2.5 |
| Ramsey (1967) | Dayton parking atttendents | 24 | 2.9 | 9.3 ± 3.16 | | +6.4 | +2.0 |
| Buchwald (1969) | Alberta garage operators | | | | | | |
| | (1-9/day) | 21 | | 6.4 | (1-15) | | +1.4 |
| | (10-20/day) | 138 | | 8.5 | (0.5-19) | | +3.5 |
| | (>20/day) | 76 | | 9.2 | (1-18) | | +9.2 |
| Breysse and Bovee (1969) | Seattle fork lift drivers | | | | | | |
| | (<20/day) | 44 | | 3.5 | (0-17) | | +2.3 |
| | (20-40/day) | 38 | | 5.5 | (1-20) | | +4.3 |
| | (>40/day) | 6 | | 6.5 | (3-14) | | +5.3 |
| Gothe, Fristedt, Sundell, Kolmodin, Ehrner-Samuel and Gothe (1969) | Stockholm policemen | 28 | | 3.5 ± 1.17 | | | +2.3 |
| | Malmo policemen | 6 | | 5.0 ± 2.4 | | | +4.2 |
| | Orebo policemen | 5 | | 2.4 ± 1.1 | | | +1.8 |
| Petrilli and Kanitz (1970) | Genoa vehicle drivers | 20 | | | (6.0-8.5) | | |
| Cohen, Dorion, Goldsmith, Permutt (1971) | US-Mexican border inspector | 11 | 4.8 | 6.4 | | +1.6 | +2.8 |
| Mean (overall for number of subjects) | | | | 6.8 (446 subjects) | | | +4.07 (446 subjec |

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This review contains a paragraph on the role of carbon monoxide in pathogenesis of atherosclerosis. The author views the problem in the proper perspective.

The manner in which cigarette smoking accelerates atherosclerosis and its complications is, in short, unexplained. It is possible that in some way cigarette smoking damages the arterial intima. Carbon monoxide is the likeliest immediate candidate for such a role. Some presently mysterious interference with the normal mechanism of transport of lipids from the plasma through the vascular tunics to the lymphatics secondary to the inhalation of cigarette smoke is an alternative possibility. In all populations yet scrutinized, the prevalence and incidence of CHD rise with the serum cholesterol concentration.[32] It is, accordingly, a plausible hypothesis that inordinate cigarette smoking may be associated with an increased serum cholesterol concentration. Such a relationship does, indeed, exist, but is unimpressive. Although the serum cholesterol concentration in both men and women is consistently higher in cigarette smokers, the influence of increasing age is substantially greater (figs. 1 and 2).[33] The observation that heavy cigarette smokers have far more atheroma than nonsmokers is, possibly, complemented by Astrup's observation that fat-fed rabbits exposed to high tensions of carbon monoxide exhibit extreme hyperlipidemia and cholesterosis as compared to controls not exposed to carbon monoxide.[3-5, 28] This interesting experimental model has, however, no recognized counterpart in human epidemiological studies. Obesity as a coronary risk factor is not related to cigarette smoking.[2] Lastly, the arterial blood pressure is not associated with cigarette habit.[2]

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Habitual smokers who also suffer from chronic lung disease are known to have an elevated carboxyhemoglobin level. Such patients show a reduction in pulmonary diffusion capacity (Chosy et al., 1963; Clauzel et al., 1966; Trinquet et al., 1971). Chevalier et al. (1966) compared such patients with nonsmokers inhaling 0.5% carbon monoxide. The resulting elevation in levels of carboxyhemoglobin caused a reduction in pulmonary diffusing capacity in nonsmokers. On this basis, it was proposed that the reduction in pulmonary diffusion capacity in smokers is due to elevation of the carboxyhemoglobin level. This explanation has not been supported by any other form of experimental data.

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## IV B. Chronic Respiratory Effects in Humans

The medical examination of traffic officers stationed at the Holland Tunnell in New York has provided an opportunity to determine the effects of chronic exposure to 70 ppm carbon monoxide. Sievers et al. (1942) examined 156 such officers and failed to find any evidence of injury to health that was attributable to carbon monoxide exposure. There were no signs or symptoms of respiratory abnormalities. Other reports of elevated carbon monoxide levels in highway tunnels have appeared, but the clinical examination of the traffic officers has not been included (Braja and Trompeo, 1964; D'Arca et al. 1964; Miranda et al., 1967; Yamate and Matsumura, 1968).

Astrup et al. (1968) and Klausen et al. (1968) exposed 8 male subjects to inhalation of 0.5% carboxyhemoglobin, resulting in a blood level of 10%. There were no changes in ventilation, circulation or metabolism.

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IV C. Acute and Chronic Respiratory Effects in Animals

The lack of respiratory stimulation during acute exposure to carbon monoxide has also been demonstrated in animals (Korner, 1965). In perfusion of the carotid body chemoreceptors there was no evidence of direct stimulation by carbon monoxide (Duke et al., 1952; Joels and Neil, 1961; Meyer et al., 1972). With extremely high levels of carboxyhemoglobin a fall in blood oxygen tension occurs, which may cause activation of chemoreceptors. However, the respiratory centers are depressed directly by the reduction in blood oxygen content, so that chemoreceptor-induced hyperpnea is not apparent (Mills and Edwards, 1968).

Carbon monoxide in a concentration of 2% provokes bronchoconstriction in the guinea pig (Parrot et al., 1971). In the cat lung, ventilation with 1 to 20% carbon monoxide in air caused bronchodilatation with a fall in pulmonary arterial pressure (Duke and Killick, 1952). In the dog there is a rise in pulmonary arterial blood pressure following inhalation of carbon monoxide (Rubino, 1964). The differences in bronchomotor and pulmonary vascular responses between animal species have not been explained. Carbon monoxide is not toxic to bronchial cilia of various animals (Okeson and Divertie, 1970).

There are other differences in responses of various animal species. In the rat lung, exposure to 0.5 or 1.0% carbon monoxide in air caused swelling of alveolar epithelial mitochondria and nucleoplasm, swelling of capillary endothelial cells and capillary platelet thrombosis (Niden and Schulz, 1965). Mice exposed to carbon monoxide showed similar alteration

in the alveolar tissue (Bils and Romanovsky, 1967; Rhodes, 1971). Experiments on the dog indicate that adminstration of a mixture of 8% to 14% carbon monoxide did not cause ultrastructural changes in the lung that could be attributed to the gas per se (Norman et al, 1966; Fisher et al, 1969). The observations on primates do not include electron microscopy. So far, the only published report based on gross and histopathological examination of lungs and other organs of the cynomolgus monkey does not reveal any abnormalities resulting from continuous exposure to 19.86 and 65.46 ppm carbon monoxide for 2 years (Eckardt et al, 1972).

The chronic exposure of animals to cigarette smoke reported by Dontenwill et al, (1966); Dontenwill (1967, 1970), and by Campbell (1936) does not relate directly to the effects of carbon monoxide alone. Experiments regarding exposure to automobile exhaust reported by Vaughan et al (1969) are difficult to interpret in terms of identifying the effects of carbon monoxide. Chronic exposure to carbon monoxide in air caused an aggravation of pulmonary tuberculosis in rabbits (Kiriachko, 1966) and did not influence the rate of tumor development in rats (Shintani, 1968).

## IV. RESPIRATORY SYSTEM

### C. Acute and Chronic Respiratory Effects in Animals

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## V. CIRCULATORY SYSTEM

The investigation of circulatory effects of carbon monoxide has been more extensive than that of its effects on the respiratory system discussed in the preceding section. There has been increasing concern that chronic exposure to carbon monoxide present in cigarette smoke would lead to diseases of the heart and blood vessels and abnormalities in the composition of the blood. However, the problem has not been solved by direct experimentation relating to the carbon monoxide in cigarette smoke. There are numerous observations regarding the effects of sublethal concentrations of carbon monoxide in man and animals. These are reviewed in the following paragraphs, although they are only remotely related to the small amount of carbon monoxide contained in cigarette smoke.

### V A. Heart Rate

The acceleration of heart rate known to occur during inhalation of cigarette smoke is explained by the nicotine content. The amount of carbon monoxide in the smoke does not influence heart rate, since experiments consisting of administering carbon monoxide alone in amounts even exceeding that produced by cigarettes failed to alter the electrocardiogram.

The electrocardiograms of patients suffering from acute carbon monoxide poisoning or chronic exposure to carbon monoxide show the following alterations: depression of S-T segment (Steinmann, 1937; Störmer, 1938; Wendt, 1941; Graybiel, 1942; Breu, 1943; Patz, 1949; Saracoglu, 1951); sinus arrhythmia (Breu, 1942); premature systole (Parade and Franke, 1939); atrial flutter

(Donatelli, 1940; atrial fibrillation (Dvorak et al., 1951; Cosby and Bergeron, 1963); distortion of QRS-T complex (Hegglin, 1944; Kostyukova, 1951; Lorente and Varela de Seijas, 1953) Wolff-Parkinson-White syndrome (Doumer and Merlen, 1946; Seling, 1966); atrioventricular block (Ehrich et al., 1944; Altmann, 1953; Kledecki and Winiarski, 1963); bundle-branch block (Graziani et. al., 1957); and cardiac arrest (Brunner, 1939). Multiple abnormalities in the electrogram have been reported (Faivre et al., 1954; Faivre et al., 1959; Capellaro and Gandolfo, 1964; Hayes and Hall, 1964; Medvedowsky et al., 1965; Shafer et al., 1965; Zanardi et al., 1966; Kuroiwa et al., 1968; Orinius, 1968; Lang et al., 1969; Mosinger et al., 1969; Lustman and Geerts, 1971; Thiels et al., 1972). Most of these abnormalities have been reproduced in animals inhaling concentrations larger than 2% carbon monoxide in air (von Bergmann, 1934; Motta, 1940; Loeper et al., 1942; Lewey and Drabkin, 1944; Hundt and Grünberg, 1960; Mainardi, 1964; Datsenko, 1966; Mosinger et al., 1969)

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#### A. Heart Rate

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The rat has been the laboratory animal most extensively used to investigate myocardial effects of carbon monoxide. Asmussen and Paulsen (1953) exposed immature rats for 60 days to an atmosphere containing carbon monoxide. The blood levels were kept at 50 to 60% carboxyhemoglobin. Compared with control rats, the carbon-monoxide-treated rats were inferior in their ability to swim till exhausted and to withstand low oxygen tension. The carbon-monoxide-treated rats showed cardiac hypertrophy and a slight but significant increase in the relative number of coronary capillaries. Suzuki (1969) administered 1% carbon monoxide for 10 min to mature rats and the animals were sacrificed from 10 min to 24 hours after cessation of inhalation. The electron microscopic examination of the heart revealed intracellular edema, swelling of mitochondria and sarcoplasmic reticula, disruption and reduction of cristae, disappearance of mitochondria, appearance of lipofuscin pigment granules and lysosomes and increase of glycogen granules and fat droplets. The author concluded that the effects of carbon monoxide on the heart result not only from hypoxemia but also from the direct toxic effects on the specific respiratory enzymes.

Holczabek (1971) arrived at a similar conclusion following exposure of rats to 3% carbon monoxide. Slater (1950) demonstrated inhibition of dihydrocozymase oxidase of heart muscle exposed to carnon monoxide in vitro.

The direct effects of carbon monoxide on the monkey heart have not been investigated. Since there is a species difference relating to pulmonary effects, it is reasonable to suspect that this may also apply to the heart. The rabbit heart shows cardiac necrosis, which could be interpreted to be the result of hypoxemia rather than the direct effect of carbon monoxide (Veith, 1940)..

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### B. Myocardium


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## V C. Coronary Circulation

In recent years there has been an increasing number of publications associating coronary heart disease with the carbon monoxide contained in cigarette smoke (Jaffe, 1968; Dinman, 1969; Robin et al., 1969; Goldsmith, 1970; Szöllösi et al., 1970; Tibblin, 1971; Schievelbein and Eberhardt, 1972; Marland and Bersay 1972). The evidence for stating that the carbon monoxide content of cigarette smoke caused coronary heart disease is indirect. A review of the investigations concerned reveals that the levels of carboxyhemoglobin in the blood of habitual smokers do not cause coronary heart disease.

The effect of exposure to lower concentrations of carbon monoxide in high-pollution areas of Los Angeles has been examined by Cohen et al. (1969). The case fatality rates for patients admitted with myocardial infarction to 35 hospitals during 1958 were examined. The results indicate that there was an increase in fatality rate in high-pollution areas and that this difference was evident during periods of relatively increased carbon monoxide pollution. However, it was not possible to prove cause and effect relationship between carbon monoxide and high fatality rate, since there are other pollutants involved. In the same city, Haywood et al. (1972) examined 34 patients with acute myocardial infarction and 35 control patients with diverse diseases. Carboxyhemoglobin levels averaged 5.14 % for the infarct patients and 4.8 % for the controls; there was no clear-cut relationship between carbon monoxide levels and acute infarction. For patients with angina pectoris, exposure to the heavy morning freeway traffic in Los Angeles

caused a decrease in exercise performance that initiated the onset of angina (Aronow et al., 1972). The mean blood levels of carboxyhemoglobin in % were 1.12 ± 1.20 before, 5.08 ± 1.19 immediately after leaving the freeway, and 2.91 ± 0.93 two hours later. Any one of the pollutants other than carbon monoxide may be responsible for quicker development of angina after less cardiac work. Ten patients with angina pectoris were examined by Aronow and Rokaw (1971) and Aronow et al. (1971) following the smoking of low-nicotine cigarettes. After each subject had smoked 8 cigarettes, at the rate of one every 30 min, the carboxyhemoglobin level in the blood rose from 1.58 to 7.79%. This was accompanied by a decrease in exercise tolerance. These results cannot be interpreted to mean that carbon monoxide alone is the cause of the decrease in exercise tolerance. The only direct proof would be to repeat similar observations on patients inhaling carbon monoxide mixture. De Bias et al. (1972) exposed dogs with myocardial infarction to 100 ppm carbon monoxide for 14 weeks. The elevation of the blood carboxyhemoglobin level to 14% did not influence the electrocardiogram nor the serum enzymes that would be expected to accompany increasing severity of hypoxia. Carbon monoxide alone, producing up to 14% saturation of carboxyhemoglobin, does not appear to exaggerate myocardial infarction in dogs.

Exposure of rabbits for up to 14 months, resulting in a blood level of 15 to 40% carboxyhemoglobin, causes myocardial damage (Andersson, 1972). The lesions are similar to those reported for patients who have recovered from acute carbon monoxide poisoning. Some of these patients manifested anginal

attacks (Kroetz, 1936a; Beck and Suter, 1938; Hubert, 1943; Zeh, 1960) and myocardial infarction (Kroetz, 1936b; Wiktor, 1954: Anderson et al., 1967).

The effects of inhalation of 0.1 or 5% carbon monoxide, sufficient to raise the carboxyhemoglobin level to between 5 and 25% in dogs and humans, were reported by Ayres et al. (1969, 1970). There was an increase in coronary blood flow and alteration of lactate and pyruvate metabolism. Most of these changes could be accounted for by hypoxemia, although a direct effect of carbon monoxide on the coronary vessels has not been excluded.

V. CIRCULATORY SYSTEM

C. Coronary Circulation

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V D. Systemic Circulation

Cigarette smoking causes vasoconstriction of most vascular beds. These effects are brought about by nicotine contained in the smoke. The carbon monoxide absorbed during smoking does not contribute to the vascular effects. In animals, the pattern of action of carbon monoxide is vasodilatation with elevation of body temperature (Binet and Burstein, 1948; Coret and Hughes, 1964; Nielsen, 1971).

Acute carbon monoxide poisoning is accompanied by a fall in aortic blood pressure (Litzner, 1936; Deviatka, 1956; Navratil, 1956; Vyskocil and Novotny, 1956; Chudzikiewicz, 1957; Mihai and Weber, 1964; Heidrich et al., 1970). Hypotension has also been noted following exposure to carbon monoxide in dogs (Brewer, 1937; von Oettingen et al., 1941), cats (Kayser, 1939; Maurer, 1941), rabbits (Nishigori, 1932; Süpfle, 1934) and rats (Truhaut et al., 1968). The fall in blood pressure is entirely due to vasodilatation, which has been demonstrated in dogs (Sulotto et al., 1969 a and b). In man vasoconstriction of the hand reflexly induced by cold is reduced by levels of 19 and 25 % carboxyhemoglobin (Heistad and Wheeler, 1972).

The influence of carbon monoxide on capillary permeability has been investigated in humans and animals. In man, exposure to carbon monoxide for 8 days caused an increase in the permeability of the capillaries to albumin (Siggaard-Andersen et al., 1968, 1969). The increase in permeability could not be demonstrated in the calf muscle (Petersen et al., 1968). In rabbits, guinea pigs and rats there is an increase in permeability in the peritoneal cavity (Göthert et al., 1970) and subcutaneous tissue (Van Liew, 1968 a and b, 1970).

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## V. CIRCULATORY SYSTEM

### D. Systemic Circulation

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## V E. Arteries

Although no specific case of arterial disease caused by carbon monoxide associated with cigarette smoking has been reported, there have been repeated suggestions of cause and effect relationship. The facts are as follows:

1. Patients who have been exposed to acute carbon monoxide poisoning develop skeletal muscle necrosis. (Mautner, 1955), Volkmann's contracture Ortizaga, 1967) or venous thrombosis (Heidrich and Klems, 1969). Similar lesions have not been reported following exposure to low levels of carbon monoxide.

2. In patients with thromboangiitis obliterans or Buerger's disease, Astrup (1964) pointed out a connection between smoking and increased affinity of hemoglobin. Astrup (1966 a and b) and Astrup et al. (1966) showed the increase in affinity for oxygen to be associated with carbon monoxide present in tobacco smoke, since higher carboxyhemoglobin levels were observed in smokers with thromboangiitis obliterans than in healthy smokers. Mulhausen et al. (1967) confirmed this observation in another group of patients. Kjeldsen and Mozes (1969) and Kjeldsen (1969) noted in a third group of patients that the carboxyhemoglobin saturations and cholesterol levels are higher in controls. Birnstingl et al. (1966) demonstrated that patients with thromboangiitis obliterans did not show a greater alteration in oxygen affinity produced by smoking than did compared with normal smokers. The possibility that carboxyhemoglobin increases blood viscosity and therefore reduces the velocity of blood circulation and hastens the tendency to thrombus formation, has been excluded by measurements performed by Sølvsteen and Kristjansen (1968).

3. That exposure to carbon monoxide could lead to arteriosclerosis was proposed by Hueper (1944) as part of his anoxemia theory. Astrup and his collaborators have attempted to find experimental support for this theory in cholesterol-fed rabbits – see reviews by Astrup (1967, 1969, 1970, 1972) and by Astrup and Kjeldsen (1970). The exposure to carbon monoxide enhanced the development of atheromatosis (Astrup et al., 1970 a and b). The appearance of lesions was accompanied by elevation of serum lipid levels (Truhaut et al., 1968; Kjeldsen, 1970a), change in lactate dehydrogenase isoenzymes of the aortic arch (Hellung-Larsen et al., 1968), increased endothelial permeability (Wanstrup et al., 1969), and ultrastructural intimal changes (Kjeldsen et al., 1972). In human subjects exposed to carbon monoxide, an increase in capillary filtration rate (Siggaard-Andersen et al., 1967) and elevation of serum lipid levels (Kjeldsen and Damgaard, 1965, 1968; Kjeldsen, 1970b) have been demonstrated. It has been suggested that carbon monoxide inhibits synthesis of cholesterol, leading to accumulation of lanosterol (Gibbons and Mitropoulus, 1972). Another effect of carbon monoxide is an increase in mitochondrial enzymic activity, which stimulates lipid synthesis within the artery (Whereat, 1970). It has not been possible to develop atherosclerosis in animals exposed to carbon monoxide without supplemental cholesterol feeding.

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4. Examination of individuals who have been exposed to an environment of up to 1,000 ppm carbon monoxide with carboxyhemoglobin levels of blood between 2 and 26% for an average duration of 10.5 years did not reveal any early development of arteriosclerosis (Prerovská and Drdková, 1967 a and b;

1971). The average values of serum lipid levels did not exceed the normal range. The results of experiments on rabbits do not apply to epidemiologic surveys in humans.

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V F. Blood Cells and Plasma

Exposure to carbon monoxide causes an increase in platelet adhesiveness in atherosclerotic patients (El-Ebrashy et al, 1967) and in rabbits (Birnstingl et al, 1971). There is also an increase in fibrinolytic activity in patients suffering from carbon monoxide poisoning (El-Attar, 1968 a and b) and in experimental animals (Candura and Craveri, 1964). However, none of these effects have been encountered as a result of cigarette smoking.

The concentration of enzymes in the blood reflecting cardiac and liver damage have been reported in patients suffering from acute carbon monoxide poisoning (Ricci et al, 1964; Van Vugt, 1968; Duplay et al, 1967; Afans'ev, 1967; Gramer and Ruof, 1968; Müller and Voigt, 1968; Prellwitz et al, 1970; Antos and Sevcik, 1971).

Four groups of situations are characterized by a similar hematologic response. They are as follows:

1. Exposure to carbon monoxide in man causes an increase in the red cell and reticulocyte counts and the serum globulin fraction (Coscia et al, 1964; Tkachenko et al, 1966; Glass et al, 1968; Kjeldsen and Damgaard, 1968; Bethlenfalvay, 1971a). The erythrocytes manifest some differences from normal erythrocytes in staining (Blackmore, 1970; Bethlenfalvay, 1971b), denaturation of hemoglobin (Perrelli et al, 1970) and a change in the shape of the oxyhemoglobin dissociation curve to the left (Brody and Coburn, 1969).

2. In dogs, exposure to carbon monoxide increases hemoglobin

concentration (Asmussen and Vinther-Paulsen, 1949). This change is regarded as an important mechanism for tolerance or acclimatization to carbon monoxide (Otis, 1970). A similar increase in hemoglobin and the red cell count has been noted in other species, such as rabbits (Truhaut et al., 1968), rats (Ramsey, 1969), rhesus monkeys (Theodore et al., 1971), and squirrel monkeys (Jones et al., 1971).

3. Cigarette smoking causes an increase in the red cell count and
in the content of these
hemoglobin, whereas abstinence caused a fall/in humans (Eisen and Hammond,
in
1956; Pincherle and Shanks, 1967) and/hamsters (Reckzeh and Dontenwill, 1970). In another investigation involving smokers, the elevated hemoglobin and red cell count were correlated with carboxyhemoglobin levels (Petrovic, 1970). A shift in the oxygen dissociation curve to the left has been noted in cigarette smokers (Gutenkauf et al. 1967; Birnstingl et al., 1967).

4. Patients suffering from myocardial ischemia with normal coronary arteriograms have been shown to have abnormal hemoglobin-oxygen dissociation (Likoff et al., 1967; Eliot and Bratt, 1969; Guy et al., 1971). There is no evidence that these patients sustain carboxyhemoglobinemia, nor is the ischemia associated with cigarette smoking.

The above examples are clearly different entities. Cigarette smoking is included only in situation 3 and carbon monoxide in 1 to 3.

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## VI B. Eye and Visual Pathways

Visual threshold is influenced by administration of carbon monoxide (see review by McFarland, 1970). McFarland et al. (1944) used a visual discriminometer and noted a change in visual sensitivity following exposure to 0.01% carbon monoxide. There was a fall in threshold with a rise of 5% in carboxyhemoglobin level in 2 subjects. Lilienthal and Fugitt (1946) noted in 5 subjects that increments of 5 to 10% carboxyhemoglobin impaired the critical flicker fusion frequency. Halperin et al. (1959) observed the recovery from the effects of carbon monoxide on visual function. Administration of pure oxygen resulted in an immediate improvement, and the addition of 7% carbon dioxide to the oxygen hastened the elimination of carbon monoxide from the body, compared with the inhalation of air.

In patients suffering from carbon monoxide poisoning the following effects have been reported: change in optically evoked response in the electroencephalogram (Helmchen and Künkel, 1964; Hosko, 1970); impairment of visual perception relating to lesions in the occipital lobe (Kuroiwa et al., 1967; Szliwowski and Klees-Delange, 1970), visual agnosia (Zolotukhin, 1968; Benson and Greenberg, 1969), retinopathy (Heydenreich, 1970; Bilchik et al., 1971) and conjunctival hemorrhages (Prokop and Wabnitz, 1970).

In laboratory animals inhalation of carbon monoxide leads to lesions which relate to those observed in human poisoning. In rabbits there is sludging of blood in the ophthalmic vessels (Taccola et al., 1965). Diminution of evoked potentials in the visual pathways occurs in cats (Ikeda, 1969) and in

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VI C. Hearing and Auditory Pathways

The auditory and vestibular apparatus is less sensitive than the eye to carboxyhemoglobin. Tibbling (1969) tested 25 human volunteers by the smoking of cigarettes. A rise in the blood level of carboxyhemoglobin to 2.5% did not influence vestibular nystagmus. Guest et al. (1970) administered carbon monoxide to produce levels of 10% carboxyhemoglobin in 8 subjects. No depression of the auditory flutter fusion threshold or of the critical flicker fusion threshold occurred. In the same subjects the oral administration of phenobarbital depressed both thresholds.

Patients suffering from acute carbon monoxide poisoning develop the following disorders relating to the ear: abnormalities in hearing (Taniewski and Kugler, 1964a; Hansz and Styperek, 1968; Kawamura, 1971); deafness (Morris, 1969; Fortunato and Catalano, 1970); distortion of the audiometric curve (Taniewski and Kugler, 1964b; Fritsche, 1969); and disturbance in cochleovestibular function (Cis and Perani, 1964; Mounier-Kuhn et al., 1968). Industrial workers exposed chronically to carbon monoxide develop similar abnormalities in hearing and vestibular function (Stanković et al., 1964; Strzelczyk and Zenk, 1964; Zenk, 1964, 1965; Sato, 1966; Mesolella et al., 1970.

In experimental animals the administration of carbon monoxide causes interference with the auditory and olfactory systems. There is depression of action potentials in the olfactory bulb of the cat (Hall, 1970) and in the cochlea of the guinea pig (Freigang et al., 1968). The morphologic examination of the inner ear shows degeneration in the rabbit (Kittner, 1968) and in other animal species (Kittel and Theissing-Erlangen).

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## VI D. Behavior of Man

The effects of carbon monoxide on human behavior have been summarized by McFarland (1952), Beard and Grandstaff (1970) and LaVerne (1970). Several reports have appeared which determine the blood level of carboxyhemoglobin that would influence functions of the higher centers of the central nervous system in man. The results are as follows:

1. Sayers et al, (1929) summarized the findings of an investigation in which 6 men were exposed for 4 to 7 hours daily over a period of 68 days to gasoline engine exhaust gas-air mixtures. Exposure to 200 ppm carbon monoxide, resulting in blood levels of 20% carboxyhemoglobin, caused frontal headache in 3-1/2 to 4 hours. Exposure to 300 ppm, producing a blood level of 30%, caused frontal and occipital headaches and vertigo after 3 hours. Nielsen (1971) in another group of subjects with 25% to 33% carboxyhemoglobin noted an elevation of body temperature.

2. The control precision and multiple limb coordination are impaired when the concentration of carboxyhemoglobin in the blood exceeds 5% (Trouton and Eysenck, 1961).

3. Psychomotor abilities are sensitive to the presence of carboxyhemoglobin. Ability to discriminate is altered at levels below 5%, while reaction time, static steadiness and muscle persistence are measurably altered by concentrations of up to 20% (Schulte, 1963). There was no difference between the test results in nonsmokers and those in smokers.

4. The ability of subjects to estimate time intervals of 1, 3 and 5 seconds was not impaired by exposures to as much as 20% carboxyhemoglobin.

Levels between 20 and 30% caused interference with visual evoked response and impairment of manual dexterity (Stewart et al., 1970).

5. Estimation of time and tracking performance was not influenced by exposure to 125 ppm carbon monoxide with a mean of 6.64% carboxyhemoglobin (Hanks, 1970; Mikulka et al., 1970; O'Donnell et al., 1970, 1971 a and b).

6. Levels of carboxyhemoglobin below 10% influence the results of tests for automobile driving performance (Ray and Rockwell, 1970).

7. Levels of 6.6% carboxyhemoglobin caused a reduction in the ability of the subjects to identify signals. This effect on vigilance did not appear with 2.3% carboxyhemoglobin (Horvath et al., 1971).

8. Exposure of students to 100 ppm carbon monoxide for 2½ hr, with mean levels of 7.2% carboxyhemoglobin, resulted in diminution of manual dexterity, visual perception and ability to learn and perform certain intellectual tasks (Bender et al., 1971). There was no discernible difference between smokers and nonsmokers with regard to their psychological susceptibility.

9. Ramsey (1972) exposed 20 normal subjects and 20 patients with pulmonary emphysema and 20 with anemia to inhalation of 0.03% carbon monoxide in air for 40 min. The mean increase of 4.5% in carboxyhemoglobin caused a diminution in the speed of reaction to a visual stimulus but no significant change in tests for depth perception and for visual discrimination of brightness.

10. The only observations relating to cigarette smoking pertain to high altitude. Kratochvil et al. (1957) tested smoking at a level of 18,000 feet. There was only a slight decrement in performance of subjects when smoking while hypoxic at high altitude compared with that of the hypoxic controls. Astrup et al. (1971)

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reported on a patient who suffered from mountain sickness over many years. The attacks were provoked either by cigarette smoking or by inhalation of 0.5% carbon monoxide. There are no other reports of such patients with mountain sickness induced by tobacco smoking. It is possible that these responses may relate to changes in cerebral blood flow described by Demange and Auzas (1969).

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## VI. E. Behavior of Animals

The effects of carbon monoxide on the behavior of certain animals have been described, viz, on that of rats (Beard and Wertheim, 1967; Goldberg and Chappell, 1967; Teichner, 1967; Stupfel et al, 1968; Khachaturiyan et al, 1969; Rose et al, 1970; Stupfel and Bouley, 1970; Nečas and Neuwirt, 1971), mice (Hirata et al, 1969; Gaume et al, 1971), dogs (Carding, 1968; Preziosi et al, 1970), monkeys (Back, 1969), and laboratory animals (Fazekas, 1967). The morphologic and functional features of the brain have been described, resulting from exposure of various animals to carbon monoxide, viz, rats (Thomas and Pearse, 1964; Miyagishi and Hiyashi, 1968; Miyagishi and Suwa, 1969; Takahata and Miyagishi, 1969), mice (Estler et al, 1971A), guinea pigs (Kupfer and Wünscher, 1968), cats (Ando et al, 1969; Barrios et al, 1969), birds (Dugnat, 1965), and frogs (Segal, 1970). The brain exposed to carbon monoxide shows a reduction in content of gangliosides (Mawatari, 1970), accumulation of ammonia (Okunyev and Prokhorenko, 1965; Mishchenko and Frenkel, 1966), decrease in catecholamines (Marks and Swiecicki, 1971); decrease in serotonin (Pare et al, 1969), and decrease in glycogen (Estler et al, 1969, 1971b). The relationship of these results to the behavior pattern has not been elucidated.

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VI F. Electroencephalogram in Man and Animals

All of the available information regarding the effects of carbon monoxide on the electroencephalogram relates to high concentration of the gas in the blood. In rabbits, levels of 45% and 74% carboxyhemoglobin were used respectively by Komura (1967) and De Valois and Schadé (1967). With these high concentrations there are various effects: shortening of the hippocampal electroencephalogram, appearance of slow waves in the neocortex, hypothalamus and caudate nucleus, and increase of the threshold of the arousal reaction in the neocortex. In rats, a decrease occurs in the amplitude and frequency of electrical cortical activity (Fodor et al, 1964).

The electroencephalogram of patients who become unconscious as a result of carbon monoxide poisoning shows the following changes: appearance of slow waves (Faure et al, 1965; Revol et al, 1966; Sasaki et al, 1966); low voltage fast waves (Tatetsu et al, 1968); delta waves (Mann, 1965; Tatetsu et al, 1967a); reduction in fast waves accompanied by rapid eye movement (Karacan et al, 1971); and a decrease in cortical evoked potential to photic, somatosensory and auditory stimulation (Kuroiwa et al, 1968). Most of these abnormalities remain even for two to five years after the acute exposure to carbon monoxide (Orioli and Cattania, 1965; Geier, 1966; Inanaga et al, 1966a and b; Revol et al, 1966; Sasaki et al, 1966; De Valois and Schadé, 1967; Tatetsu et al, 1967b; Harada and Kozuma, 1968; Tomonari, 1968; Grohme et al, 1969; Yasuoka, 1970; Harada et al, 1971; Totsuka et al, 1971).

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VII. OTHER ORGAN SYSTEMS

The investigations of the effects of carbon monoxide on organs other than the respiratory, circulatory and nervous systems are reviewed in this section. Two topics are remotely related to cigarette smoking and the coverage of each is confined to a bibliographic list: the effects of carbon monoxide on hepatic cells (see additional bibliographic list no. 12) and on unicellular organisms and lower vertebrates (see additional bibliographic list no. 13).

VII. A. Renal System

Some patients with severe carbon monoxide poisoning develop acute renal failure (Burck and Portwich, 1964; Nicolas and Nicolas, 1964; Kobulniczky and Koncz, 1966; Wijdeveld, 1968; Leonowicz, 1967; Linton et al., 1968; Quintana et al., 1969; Grosse and Neuhaus, 1970; Wojczuk and Chylak, 1971). The mechanism for the development of acute renal failure is believed to be other than hypoxia alone. Pauli et al. (1968a) noted a difference in the renal function of normal subjects at a high altitude (3,454 meters above sea level) for 10 days and that of 6 subjects exposed to carbon monoxide for 10 days with a carboxyhemoglobin concentration of 15%. In the presence of carboxyhemoglobin there is an increase of glomerular filtration rate with renal plasma flow remaining unchanged. This combination was interpreted to mean constriction of the efferent vessels with dilatation of the afferent arterioles. On the other hand, hypoxia caused an increase in renal plasma flow with an accompanying change in glomerular filtration rate in the same direction. In the same group of subjects, renal tubular electrolyte handling was consistent with the primary

elevation of glomerular filtration rate during exposure to carboxyhemoglobin (Pauli et al., 1968b). There was no increase in urinary elimination of protein (Steiner et al., 1971).

## VII. OTHER ORGAN SYSTEMS

### A. Renal System

BURCK H C and PORTWICH F : Akute Niereninsuffizienz nach schwerer Kohlenmonoxyd-Intoxikation. (Acute renal failure after severe carbon monoxide poisoning.) Frankfurt Z Path 73: 520-34, 1964. 551

GROSSE G and NEUHAUS G A : Aminopeptidase-Aktivitat im Urin bei Patienten mit Hypnotica-Intoxikationen und unter den Bedingungen der Vita reducta. (Aminopeptidase activity in urine in patients with sedative poisoning and under conditions of vita reducta.) Klin Wochenschr 48: 978-85, 1970. 552

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## VII B. Pregnancy

Accidental carbon monoxide poisoning in a pregnant mother has been known to cause fetal death (Goldstein, 1965; Kells, 1969; Stokowski and Kęsiak, 1969). There is a report of a case without fetal abnormality (Larcan et al., 1970). Most other reports describe brain lesions in babies born of mothers who have suffered from carbon monoxide poisoning (Bankl and Jellinger, 1967; Kamraj-Mazurkiewicz, 1967; Szilágyi, 1967; Beaudoing et al., 1969; Matsuyama, 1969).

The diffusion of carbon monoxide across the placenta has been investigated in the sheep (Metcalfe et al., 1965; Longo et al., 1967, 1969; Longo, 1970; and Piédelièvre et al., 1969) and in humans (Gemzell et al., 1958; Friberg et al., 1959). Small quantities of carbon monoxide have been administered to pregnant women for measurement of the diffusing capacity of the placenta (Delivoria-Papadopoulos and Coburn, 1972). The radioactive form of carbon monoxide administered by inhalation has been used to localize the placenta in a mother close to parturition (Glass et al., 1968; Hakim, 1970).

Carboxyhemoglobin levels in maternal and fetal blood have been measured by several investigators (Table 7). The levels in mothers who smoked were higher than in those who were nonsmokers.

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Respiration in infants of mothers who smoked took longer to establish than in those of nonsmokers (Heron, 1962; Tanaka, 1967; Scoppetta, 1968). There was a higher incidence of prematurity among mothers who smoked (Girond, 1967) and a higher neonatal mortality rate (Comstock et al., 1971). The period of gestation is 29 to 34 hours

shorter for smokers than for nonsmokers (Buncher, 1969). The birth weight of babies born of mothers who smoked was lower (Mantell, 1964; Baribaud et al., 1970; Murphy and Mulcahy, 1971; Astrup et al., 1972).

There is a rise in carboxyhemoglobin level in the blood of the newborn. Behrman et al. (1971) have noted a mean rise of 6.98% in 16 newborn infants, which related to the level of pollution in the nursery. When the concentration of carbon monoxide exceeded 20 ppm, there was a decrease of 11.4% in the oxygen-carrying capacity during the first 24 hours and a decrease of 13.9% during the 25 to 85 hours after birth. These changes do not correlate with the history of maternal smoking and are caused by the concentration of carbon monoxide in the atmosphere.

The effect of carbon monoxide alone on the birth weight of rabbits has been investigated by Astrup et al. (1972) and in rats by Younoszai et al (1969). An exposure to 90 ppm carbon monoxide resulting in 9 to 10% carboxyhemoglobin in the blood caused a reduction in birth weight and an increase in neonatal mortality. The influence of a level of 5% carboxyhemoglobin was not investigated.

(Table 7 appears on the following page.)

Table 7. Carboxyhemoglobin levels of fetal and maternal blood.

| Reference (Year) | Nonsmoking mothers | | | Smoking mothers | | |
|---|---|---|---|---|---|---|
| | No of mothers | Maternal Mean ± SD (Range) | Fetal Mean ± SD (Range) | No of mothers | Maternal Mean ±SD (Range) | Fetal Mean ± SD (Range) |
| Haddon, Nesbitt and Garcia (1961) | 7 | (0.1-3.1) | (0.2-2.8) | 12 | (0.1-8.4) | (0.1-9.8 |
| Heron (1962) | 27 | 2.6 (0.4-4.4) | 2.5 (0.2-3.6) | 21 | 6.7 (1.6-14) | 5.0 (1.1-9.2) |
| Young and Pugh (1963) | 9 | 1.6 ± 0.42 | 1.61 ± 0.37 | 6 | 2.0 ± 0.77 | 2.4 ± 0.74 |
| Bjure and Fällström (1963) | 8 | 1.0 (0.7-1.43) | 1.15 (0.77-1.64) | | | |
| Younaszai, Kacic and Haworth (1968) | 11 | 1.2 (0-3) | 0.[illegible] (0-1.5) | 10 | 8.3 (2-12) | 7.3 (2-10) |
| Cole, Hawkins and Roberts (1972) | 129 | 1.2 (0-2.4) | 2.2 | 93 | 4.1 (0.5-14) | 7.5 |
| Astrup, Trolle, Olsen and Kieldsen (1972) | 884 | 0.87 | | 824 | 1.92 | |

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VII. OTHER ORGAN SYSTEMS

B. Pregnancy


| | Reprint |
|---|---|
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| BANKL H and JELLINGER K : Zentralnervose Schaden nach fetaler Kohlenoxydvergiftung. (Central nervous system injuries following fetal carbon monoxide poisoning.) Beitr Path Anat 135: 350-76, 1967. | 564 |
| BARIBAUD L, YACOUB M, FAURE J, MALINAS Y and CAU G : L'oxycarbonémie de l'enfant né de mére fumeuse. (Blood carbon monoxide in children born of smoking mothers.) Med Leg Domm Corpor Paris 3: 272-4, 1970. | 565 |
| BEAUDOING A, GACHON J, BUTIN L P and BOST M : Les conséquences foetales de l'intoxication oxycarbonée de la mere. (Fetal consequences of carbon monoxide poisoning of the mother.) Pediatric 24: 539-53, 1969. | 566 |
| BEHRMAN R E, FISHER D E and PATON J : Air pollution in nurseries: Correlation with a decrease in oxygen-carrying capacity of hemoglobin. J Pediatr 78: 1050-4, 1971. | 567 |
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| BUNCHER C R : Cigarette smoking and duration of pregnancy. Am J Obstet Gyn 103/7: 942-6, 1969. | 569 |
| COLE P V, HAWKINS L H and ROBERTS D : Smoking during pregnancy and its effects on the fetus. J Obstet Gyn 79: 782-7, 1972. | 570 |
| COMSTOCK G W, SHAH F K, MEYER M B and ABBEY H : Low birth weight and neonatal mortality rate related to maternal smoking and socioeconomic status. Am J Obstet Gyn 111: 53-9, 1971. | 571 |
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VII C. Endocrine System

The sex organs in animals influence the survival rate in carbon monoxide exposure. Stupfel et al. (1971) noted a higher mortality in male than in female mice and that castration increased the mortality in the female. The mechanism by which estrogens and progestogens increase the tolerance to carbon monoxide poisoning is not known. On the other hand, carbon monoxide in vitro depresses some of the enzymes that are involved in the biosynthesis of estrogen (Meigs and Ryan, 1971). The structure of the ovary was unaffected and all the stages in the development of the ova were noted in rats exposed to carbon monoxide in vivo (Mamatsashvili, 1970). The effects of carbon monoxide on male fertility are uncertain (Wittgens, 1966).

Adrenalectomy increased the mortality of rats and mice in response to carbon monoxide (Pukhov, 1964). In animals with adrenals intact, adrenal cortical activity is stimulated by exposure to carbon monoxide (Katsuki et al., 1966; Hanke and Kiereś, 1967). Stimulation of the adrenal medulla also occurred, which contributed to the hyperglycemia (Bour et al., 1968; Hirano et al., 1968). There are substances in the rat adrenal gland which combine with carbon monoxide (Harding et al., 1964; Wilson and Harding, 1970). The role of these substances in mediating the stimulation of the adrenal gland and in reducing the lethality of carbon monoxide has not been considered. The reduction in rate of growth of rats exposed to carbon monoxide is associated with a decrease in activity of the thyroid gland (Truhaut et al., 1965; Pogrund, 1969).

The inhalation of carbon monoxide in human subjects causes an

elevation of blood sugar (Hirano et al, 1967; Nakao, 1969). The hyperglycemia induced by cigarette smoking is believed to be due to nicotine stimulation of the adrenal medulla (Haggard and Greenberg, 1934). The contribution of carboxyhemoglobin derived from cigarette smoking has not been estimated.

VII. OTHER ORGAN SYSTEM

C. Endocrine System

| | Reprint |
|---|---|
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| KATSUKI S, ANDO and NISHIDA Y : (Diurnal variations in blood 11-OHCS level in acute carbon monoxide poisoning.) Clin Endocr Tokyo 14: 475-8, 1966. | 606 |
| MAMATSASHVILI M I : On the detrimental effect of carbon monoxide and sulfur dioxide on fertility of female rats. Hyg Sanit 76: 277-9, 1970. | 607 |
| MEIGS R A and RYAN K J : Enzymatic aromatization of steroids. I. Effects of oxygen and carbon monoxide on the intermediate steps of estrogen biosynthesis. J Biol Chem 246: 83-7, 1971. | 607 |
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| WILSON L D and HARDING B W : Studies on adrenal cortical cytochrome P-450. IV. Effects of carbon monoxide and light on cholesterol side chain cleavage. Biochemistry 9: 1621-5, 1970. | 613 |
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VII D. Bone, Muscle and Skin

There is a deposition of bone in soft tissues in patients who suffer from carbon monoxide poisoning (Ri, 1966; Mouren et al., 1972). The mechanism for this deposition is not known. In the laboratory, carbon monoxide has been used as a tool to test the polarizing power of bone mineral (Nash and Beebe, 1969).

Some patients suffering from acute carbon monoxide poisoning develop contractures of the skeletal muscle (Howse and Seddon, 1966; Kolb, 1968). Three factors contribute to the development of contracture: (1) ischemia due to reduction in blood oxygen content; (2) hyperexcitability of neuromuscular junction (Paris, 1964); and (3) binding of myoglobin with carbon monoxide (Rossi-Fanelli and Antonini, 1958; Wittenberg et al., 1965; Gladyshevskaia et al., 1966; Coburn and Mayers, 1971; Rudolph et al., 1972).

The cutaneous lesions in a patient with carbon monoxide poisoning are varied. They include bullae, subepidermal vesicles, intracellular edema and occlusion of the epidermal portion of sweat ducts (Jopkiewicz et al., 1965; Long, 1969; Leavell et al., 1969; Ippen and Goerz, 1969; Baden, 1970; Achten et al., 1971). Erythema of the face associated with a cherry-red color of the blood is a classical diagnostic sign of poisoning with carbon monoxide (Danto, 1964).

## VII. OTHER ORGAN SYSTEMS

### D. Bone, Muscle and Skin


| | Reprint |
|---|---|
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| COBURN R F and MAYERS L B : Myoglobin $O_2$ tension determined from measurements of carboxymyoglobin in skeletal muscle. Am J Physiol 220: 66-74, 1971. | 617 |
| DANTO B L : The man with a red face. Am J Psychiat 121: 275-6, 1964. | 618 |
| GLADYSHEVSKAI A T N, DOLOSHITSKY L M and SOBCHUK B A : (Myoglobin in intoxication of the organism with carbon monoxide.) Ukr Biokhim Zh 38: 9-13, 1966. | 619 |
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| KOLB K P : Lokale ischamische Kontrakturen der Hand nach Suizidversuchen. (Local ischemic contractures of the hand following suicide attempts.) Münch Med Wochenschr 110: 1873-4, 1968. | 624 |
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| NASH R J and BEEBE R A : Heats of adsorption of carbon monoxide on bone mineral and on thorium oxide by gas-solid chromatography. J Colloid Interface Sci 31: 343-52, 1969. | 628 |
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| RI K : (Case of metaplastic ossification in carbon monoxide poisoning.) Orthop Surg Tokyo 17: 397-403, 1966. | 630 |
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| RUDOLPH S A, BOYLE S O DRESDEN C F and GILL S J : A calorimetric study of the binding of carbon monoxide to myoglobin. Biochemistry 11: 1098-101, 1972. | 632 |
| WITTENBERG B A, BRUNORI M, ANTONINI E, WITTENBERG J and WYMAN J : Kinetics of the reactions of aplysia myoglobin with oxygen and carbon monoxide. Arch Biochem | |


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## VIII. CARBON MONOXIDE POISONING

It is rather a remote possibility that cigarette smoking may cause death by carbon monoxide poisoning. , There are publications on the diagnosis and treatment of carbon monoxide poisoning, both accidental and industrial. The additional bibliography lists relate to the following topics:

Accidental poisoning involving carbon monoxide and other causative factors (no. 14).

Accidental poisoning involving carbon monoxide (no. 15).

Industrial poisoning involving carbon monoxide (no. 16).

Therapy of carbon monoxide poisoning (no. 17).

Therapy of poisoning by use of normobaric and hyperbaric oxygen (no. 18).

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151 (20) BANYAI A L : Ominous misalliance: Inhalation of carbon monoxide from motor vehicles and cigarettes. Chest 58: 532, 1970. 653

153 (21) BARTLETT D Jr : Pathophysiology of exposure to low concentrations of carbon monoxide. Arch Environ Health 16: 719-27, 1968. 654

154 (22) CAMM A J : The effects of smoking. Guy Hosp Gaz 81: 185-203, 1967. 655

155 (23) CONROY J P : Smoking and the anesthetic risk. Anest Anal 48: 388-400, 1969. 656

156 (24) CURPHEY T J : Carboxyhemoglobin in relation to smoking. Nat Cancer Inst Monogr 28: 231-5, 1968. 657

160 (25) DINMAN B D : Carbon monoxide and cigarette smoking. JAMA 212: 1785, 1970. 653

162 (26) DOYLE J T : Smoking and myocardial infarction. Circulation 39 and 40: Suppl 4: 136-43, 1969. 659

163 (27) GIEL B G : Air pollution and your lungs. Pub Health News 46: 246-53, 1965. 660

164 (28) GOLDSMITH J R : Carbon monoxide and coronary heart disease. Ann Int Med 71: 199-201, 1969. 661

165 (29) GOLDSMITH J R : Carbon monoxide and coronary heart disease: compelling evidence in angina pectoris. Ann Int Med 77: 808-10, 1972. 662

166 (30) GOLDSTEIN R E and EPSTEIN S E : Medical management of patients with angina pectoris. Prog Cardiovas Dis 14: 360-98, 1972. 663

167 (31) LINDQUIST V A Y : Carbon monoxide: Its relationship to air pollution and cigarette smoking. Publ Health London 86: 20-6, 1970. 664

168 (32) NAHUM L H : Smoking and thrombosis. Conn Med 29: 853-4, 1965. 665

169 (33) NAHUM L H : Toxic products in cigarette smoke: pleasure or poison. Conn Med 32: 154-5, 1968. 666

170 (34) NAHUM L H : The effects of carbon monoxide on human health. Conn Med 33: 90-2, 1969. 667

172 (35) ROSE E F and ROSE M : Carbon monoxide: A challenge to the physician. Clin Med 78: 12-21, 1971. 668

174 (36) SELTZER C C : The effect of cigarette smoking on coronary heart disease. Arch Environ Health 20: 418-23, 1970. 669

(1) SMOKING AND HEALTH: Report of the Advisory Committee to the Surgeon General of the Public Health Service, 344-5, 1964.

## SMOKING AND ACCIDENTS

Smoking has been associated with a variety of accidents. Among these, fires have the most obvious and important consequences.

In a special study of home accident fatalities in 1952 through 1953, the Public Health Service and the National Safety Council reported that 231 (18%) of 1,274 deaths from fires of known origin were due to cigarettes, cigars or pipes (1).

The Metropolitan Life Insurance Company reported that of 352 deaths in 1956 and 1957 among their policyholders from fires and burns with known causes in and about the home, 57 (16%) were due to smoking (2).

Of physiological responses related to driving, smoking degrades detectably only the differential brightness threshold and this effect increases with
a amount of smoking (4). The epidemiological data available on the effects of smoking on traffic accidents are inconclusive.

b It has been shown that a level of carboxyhemoglobin of 5 percent—a level which is not uncommon among heavy cigarette smokers (3, 6)—depresses visual perception to as great an extent as anoxia at 8,000 to 10,000 feet altitude (4, 5).

1. Home Accident Fatalities: 1952-1953. National Office of Vital Statistics, U.S. Public Health Service, 1956. Mimeographed report. Table 12.
2. How fatal accidents occur in the home. Metrop Life Insur Statist Bull 40: 6-8, November-December, 1959.
3. Larson, P. S., Haag, H. B., Silvette, H. Carboxy-hemoglobin, p. 107-110. Tobacco: Experimental and Clinical studies. Baltimore, Williams and Wilkins, 1961.
4. McFarland, R. A., Moseley, A. L. Carbon monoxide in trucks and buses and information from other areas of research on carbon monoxide, altitude and cigarette smoking. In: Conference proceedings: Health, medical and drug factors in highway safety. National Academy of Sciences—National Research Council Publication 328, 1954. Sect. 4.17-4.33.
5. McFarland, R. A., Roughton, F. J. W., Halperin, M. H., Niven, J. I. The effects of carbon monoxide and altitude on visual thresholds. J Aviat Med 15: 6, 381-94, 1944.
6. Schrenk, H. H. Results of laboratory tests. Determination of concentration of carbon monoxide in blood. Pub Health Bull 278: 36-49, 1942.



(a) The epidemiological data reported by Boeck (1948) indicate that cigarette smoking is not responsible for the occurrence of vehicular accidents and poor driving (see page 37).

(b) A more recent report by Bender et al (1971) states that exposure to 100 ppm carbon monoxide for 2-1/2 hours, with mean blood levels of 7.2% carboxyhemoglobin, diminished visual perception. There was no difference between smokers and nonsmokers with regard to their susceptibility (see page 88).

(2) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH: <u>The health consequences of smoking</u>, 62-4, 1967.

> *Carbon Monoxide Effect*
>
> The gaseous phase of cigarette smoke contains about 4 percent carbon monoxide. This quantity can increase the levels of carboxyhemoglobin saturation of cigarette smokers from 2 percent to 10 percent (*31*). The average nonsmoker, depending on environmental exposure, usually has less than 2 percent carboxyhemoglobin saturation (*10*). Since smokers of one pack or more a day may have chronically elevated carboxyhemoglobin levels of more than 4 percent (*9*), there may be appreciable differences in the carboxyhemoglobin levels between some heavy cigarette smokers and nonsmokers.

(a) The carboxyhemoglobin blood levels of cigarette smokers expressed as ranging from 2% to 10% is not an accurate statement. A survey of the literature reveals 30 investigations with an overall mean level for 2,054 smokers of 3.76% in the blood taken 4 to 12 hours after smoking. Only 30% of subjects have levels exceeding 5% (see pages 12 to 14). The peak levels after smoking one or more cigarettes had a mean of 5.26% (see page 20). A more accurate statement would be based on integration of levels taken at hourly intervals but such information is not available.

> In addition to displacing oxyhemoglobin, carbon monoxide effects a shift in the oxygen-hemoglobin dissociation curve (*2, 3, 4 5, 6*). This may result in a decreased release of oxygen at the tissue level. A series of studies (*61, 62*) has been performed on young adults to analyze the effect of cigarette smoking on carboxyhemoglobin levels, and the consequent effect on some parameters of cardiopulmonary function. An increased post exercise oxygen debt was observed after cigarette smoking as compared to controls. This, in part, may reflect not only ventilatory disturbances but also a decreased supply of oxygen in the blood due to the carbon monoxide effect, resulting in less available oxygen to meet the increased tissue demand. Similar post-exercise oxygen debts have been noted after inhalation of enough carbon monoxide to produce comparable blood levels of carboxyhemoglobin (*21*).

(b) Inhalation of carbon monoxide in man, with blood levels of 5% to 10% carboxyhemoglobin does not influence ventilation. Ayres et al (1965) used short-term exposure and Astrup et al (1968) exposure for 8 days (see pages 42 and 45).

Commentary (2): National Clearinghouse, Cont.

The consequence of the smoking/carbon monoxide effect appears to be especially important in the myocardium where relatively more oxygen is normally extracted from the coronary circulation as compared to other organ systems. (Coronary venous blood usually has an oxygen saturation of less than 25 percent, whereas blood leaving some other organs is about 75 percent saturated with oxygen (45).) Dogs were exposed to carbon monoxide to elevate their carboxyhemoglobin saturation levels (9). In response to inhalation of carbon monoxide there was an increase in coronary blood flow but a decrease in coronary arterial-venous oxygen differences. Patients with coronary heart disease were also studied following inhalation of enough carbon monoxide to elevate their carboxyhemoglobin saturation levels to the range of 5 to 12 percent (9). In response to carbon monoxide there was generally an increase in the cardiac output and the coronary blood flow in most of the patients. While the systemic arterial-venous oxygen differences varied, either increasing or decreasing, the coronary arterial-venous oxygen differences decreased, indicating a decreased oxygen extraction by the myocardial tissue despite the myocardium's increased demand for oxygen. These decreases in myocardial oxygen extraction are related to increases in the carboxyhemoglobin saturation levels. It was observed that some patients evidently could compensate by increasing their coronary blood flows adequately to supply the myocardial tissue with sufficient oxygen, as indicated by a rise in myocardial oxygen uptake in these individuals. However, the other patients with coronary heart disease, evidently more severe, could not increase their coronary blood flow rate enough to compensate for the decreased oxygen carried by the blood. This latter group of patients, even though they had increased cardiac output, had less significant increases of coronary blood flow than those noted in the first group of patients. The coronary arterial-venous oxygen differences and the myocardial tissue oxygen uptakes both decreased, indicating that the myocardial tissue oxygen demand was not being met entirely.

(c) The experiment cited in the above paragraph specifies an increase in cardiac output with a carboxyhemoglobin value of 5% to 12%. Experiments by Brody and Coburn (1969, 1970) and Klausen et al (1968) did not show an increase in cardiac output following either acute or chronic exposure of human subjects (see page 56). Experiments on animals show myocardial lesions with exposure exceeding 50% carboxyhemoglobin (see page 57).

The reduction in the amount of oxygen available to the myocardial tissue caused by the absorption of carbon monoxide from tobacco smoke may be especially critical in persons with pre-existing coronary heart disease, especially when they cannot significantly increase coronary blood flow to compensate for increased myocardial tissue oxygen demand. The carbon monoxide effect may, in part, contribute to the increased incidence of myocardial infarctions that occur in cigarette smokers. Additional research is needed.

(d) Carbon monoxide does not contribute to the increased incidence of myocardial infarction that occur in cigarette smokers. Haywood et al (1972) could not find a clear-cut relationship between carbon monoxide levels and incidence of acute infarction. De Bias et al (1972) exposed dogs with experimental myocardial infarction to 100 ppm carbon monoxide (14% carboxyhemoglobin) for 14 weeks and did not observe an increase in severity of myocardial hyposia (see page 61 and 62).

SCHULTE J H : Effects of mild carbon monoxide intoxication. Arch Environ Health 7: 524-30, 1963. 496

STEWART R D, PETERSON J E, BARETTA E D, BACHAND R T, HOSKO M J and HERRMANN A A : Experimental human exposure to carbon monoxide. Arch Environ Health 21: 154-64, 1970. 497

TROUTON D and EYSENCK H J : The effects of drugs on behavior. Handbook of Abnormal Psychology, H. J. Eysenck, Editor, Basic Books Inc., New York 634-96, 1961.

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Commentary (3) National Clearinghouse, Cont.

Anomalous hemoglobin-oxygen dissociation was noted in "heavy" cigarette smokers (more than one pack per day) without known coronary heart disease. In experiments where the amount of cigarette smoking was controlled, there appeared to be a threshold effect: more than 12 cigarettes per day caused this anomalous dissociation to occur (53). Birnstingl (9) reports finding an increased hemoglobin affinity for oxygen in smokers, which does not appear to be explained solely by the increased carboxyhemoglobin levels in smokers.

Research to further study the interrelationships of carbon monoxide to the myoglobin of heart muscle should be performed because it is possible that carbon monoxide may replace oxymyoglobin with carboxymyoglobin and disturb the oxygen-dissociation phenomena of myoglobin (88, 120, 159). The limitations of blood supply and the high energy output of heart muscle as compared to skeletal muscle may make the myoglobin impairments by carbon monoxide of possible etiologic importance in cigarette smoking and heart disease.

Hydrogen cyanide appears to be rapidly converted to thiocyanates by the body, but the absorption by the lung of cyanide from cigarette smoke might possibly result in higher serum cyanide levels in the coronary arteries than in the systemic circulation. As noted in the 1964 Report, the cyanide ion is capable of stopping cellular respiration abruptly through inactivation of cytochrome oxidase. In sublethal exposures, the cyanide ion is gradually released from its combination with the ferric ion of cytochrome oxidase, converted to thiocyanate ion and excreted in the urine. Thiocyanate blood levels in smokers are three times higher than in nonsmokers and relative differences in urinary excretion are even more pronounced. Cytochrome oxidase is very important in cellular respiration of all body cells. In view of the extremely high myocardial cellular needs for aerobic metabolism, it is possible that the cyanide ion inactivation of cytochrome oxidase also can occur in myocardial cells and be of critical importance, especially in light of other risk factors such as impaired coronary blood flow, the carbon monoxide effect, and the known increases in myocardial tissue oxygen demand caused by the smoking/nicotine-induced catecholamine release. Further research is needed to determine whether or not cyanide ions in concentrations equivalent to those found in cigarette smokers, have a harmful effect on the myocardium, in terms of both acute and chronic exposures.

(a) The statement that relates directly to cigarette smoking is that of Birnstingl is entirely wrong and has completely reversed the meaning intended by that author. In the original publication of Birnstingl, Cole and Hawkins (1967), the increased oxygen affinity of hemoglobin in the blood of smokers could be "almost entirely due to a raised carbon monoxide hemoglobin level". A copy of a summary of the article which appeared in Brit J Surg 54: 615-8, 1967, follows:

> ...lthy male subjects over 40 years of age have a ...d oxygen affinity which is greater than that of a similar group under this age. This would result in a shift to the *left* of the oxyhaemoglobin dissociation curve.
>
> Cigarette smokers also have an increased oxygen affinity, but this is almost entirely due to a raised carbon monoxide haemoglobin level.
>
> Patients with Buerger's disease have a normal oxyhaemoglobin dissociation curve, if age and smoking habits are taken into account. Furthermore, their oxyhaemoglobin dissociation does not appear to be more sensitive to the effects of cigarette smoke than normal controls...

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(27) GIEL B G: Air pollution and your lungs. Public Health News 46: 246-53, 1965.

*FACTS ABOUT SPECIFIC AIR POLLUTANTS*

*Carbon Monoxide*

Carbon monoxide is well known to all of us. Yet many smokers are unaware that approximately seven to eight percent of their hemoglobin may be bound as carboxyhemoglobin. If in the mean time, such an individual should develop vascular insufficiency to vital organs, and then be forced to breath ambient air containing 30 ppm of CO for four to six hours or gotten into an atmosphere where he would be exposed to 120 ppm CO for one hour, he would bind an additional five percent of his hemoglobin and could suffer tragic results.

The figure of 7% to 8% carboxyhemoglobin among smokers is an over-estimation. A review of the literature shows an overall mean of 3.76% for 2,054 smokers 4 to 12 hours after smoking, and a peak level of 5.26% after smoking (see pages 12 to 14 and 20 to 21).

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Commentary (4) National Clearinghouse, Cont.

Most of the references cited are review articles which are commented upon under Bartlett (page 153 ), Goldsmith (page 165 ), and Dinman (page 160 ). The only original work referred to is by Eliot et al, which is a personal communication to the National Clearinghouse.

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(5) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH: The health consequences of smoking. A report to the Surgeon General: 1971. 59-62, 1971.

CARDIOVASCULAR EFFECTS OF CARBON MONOXIDE

Carbon monoxide (CO) is a colorless and odorless gas, low levels of which have significant effects on human and animal physiology which are just now beginning to be understood. According to Wynder and Hoffmann (219), it is present in cigarette smoke in concentrations of approximately 2.9 to 5.1 percent. The concentration of CO in smoke is subject to many factors, among them the type of tobacco and the porosity of cigarette paper. The concentration of CO in smoke has been found to increase significantly toward the last puffs of the cigarette.

(a) This paragraph states the concentration of carbon monoxide in cigarette smoke but omits mentioning the fact that the smoke is diluted with atmospheric air, dead space air and alveolar air.

According to Chevalier, et al. (41), a concentration of approximately 4 percent CO in cigarette smoke will produce alveolar levels of around 0.04 percent which, equilibrated with hemoglobin, result in carboxyhemoglobin (COHb) concentrations of from 3 to 10 percent. A number of investigators have compared COHb levels in smokers and nonsmokers. Goldsmith and Landaw (73) reported the analysis of expired air samples obtained from 3,311 longshoremen. Using a regression analysis, they calculated the concentration of COHb and found that nonsmokers showed levels of 1.2 percent while those smoking over 2 packs per day had levels of 6.8 percent and that smokers of lesser amounts had intermediate levels. Occupational exposure accounted for the mean nonsmokers' level being over 1.0 percent, an unusual finding in comparison with other studies. Kjeldsen (112) interviewed and obtained blood samples from 934 CHD-free smokers and nonsmokers. The mean COHb level for 196 nonsmokers was 0.4 percent while all inhaling smokers had a mean level of 7.3 percent. All 416 cigarette smokers, regardless of inhalation or amount smoked, showed a mean level of 4.0 percent.

(b) Chevalier et al (1966), cited in the opening paragraph, did not analyze alveolar air. They expressed the opinion that 4% carbon monoxide in cigarette smoke would result in a concentration of 0.04% after dilution. Jongbloed (1939) analyzed the alveolar air of a smoker after the 4th cigarette; the peak level was 0.0031% (see page 19).

The results of Kjeldsen (1969) have been misquoted. The blood level of carboxyhemoglobin in 934 subjects free from coronary heart disease had the following mean value: 0.4% for 196 nonsmokers and 4.2% for 738 smokers. Of the latter group the 121 light smokers had a mean of 2.5%; the moderate smokers one of 4.1% and the heavy smokers one of 5.7%. The figure 7.3% appearing in the paragraph is for atherosclerotic subjects. (Tables from Kjeldsen's paper are reproduced below.)

Commentary (5) National Clearinghouse, Cont.

Table VI - 11

| Smoking cathegory | Carboxyhaemoglobin (sat. per cent) Controls M ± SD | Atherosclerotic subjects M ± SD | Significance | Serum cholesterol (mg/100 ml) Controls M ± SD | Atherosclerotic subjects M ± SD | Significance |
|---|---|---|---|---|---|---|
| Smokers | 4,2 ± 3,1 (738) | 7,0 ±3,7 (57) | p <0,001 (t = 5,52) | 247 ± 44 (738) | 290 ± 33 (57) | p<0,001 (t = 4,89) |
| Non-smokers | 0,4 ± 0,9 (196) | 0,5 ± 0,7 (2) | n.s. (t = 0,16) | 236 ± 49 (196) | 284 ± 56 (2) | p = 0,02 (t = 2,32) |

Table VI-11: Average values of carboxyhaemoglobin and serum cholesterol in smokers and non-smokers in the control group and in the group with atherosclerotic cardiovascular diseases.

n.s. = not significant at the 0,05 level.

The number of subjects in each smoking cathegory is given below the means and standard deviations.

Table VI - 12

| Smoking cathegory | Carboxyhaemoglobin (sat. per cent) Controls M ± SD | Atherosclerotic subjects M ± SD | Significance | Serum cholesterol (mg/100 ml) Controls M ± SD | Atherosclerotic subjects M ± SD | Significance |
|---|---|---|---|---|---|---|
| Light smokers | 2,5 ± 2,5 (121) | 3,7 ± 2,5 (3) | n.s. (t = 0,76) | 245 ± 38 (121) | 279 ±67 (3) | n.s. (t = 1,45) |
| Moderate smokers | 4,1 ± 3,0 (463) | 7,3 ± 3,6 (34) | p <0,001 (t = 4,95) | 246 ± 45 (463) | 286 ± 50 (34) | p<0,001 (t = 4,52) |
| Heavy smokers | 5,7 ± 3,0 (154) | 7,0 ± 4,0 (20) | n.s. (t = 1,45) | 253 ± 45 (154) | 298 ± 53 (20) | p<0,05 (t = 2,18) |

Table VI-12: Average values of carboxyhaemoglobin and serum cholesterol related to intensity of smoking in normal smokers and in smokers with atherosclerotic cardiovascular diseases.

n.s. = not significant at the 0,05 level.

The number of subjects in each smoking cathegory is given below the mean values and standard deviations.

c Carbon monoxide has many varied and significant effects on human physiology. An overall review of these effects may be found in a discussion by Lilienthal (127) or more recently in an extensive review by the United States Public Health Service National Air Pollution Control Administration (194). Apart from its effects on respiratory and circulatory function, CO has been found to affect certain central nervous system functions adversely. These effects are probably due to interference by CO with the proper oxygenation and oxidative metabolism of the tissue in question.

CO interferes with oxygen transport in a variety of ways. First, the affinity of hemoglobin for CO is approximately 200 times greater than its affinity for oxygen, and thus CO can easily displace oxygen from hemoglobin. Second, CO shifts the oxyhemoglobin dissociation curve. By increasing the avidity with which oxygen is bound by hemoglobin, CO interferes with $O_2$ release at the tissue level. This is of greatest importance at the tissue level where the oxygen content of the capillary blood has been reduced to approximately 40 percent saturation. Here the shift can substantially decrease the oxygen tension supplying the tissues.

Third, and of more recent note, is the possible interference by CO with the homeostatic mechanism by which 2, 3-diphosphoglycerate (2, 3-DPG) controls the affinity of hemoglobin for oxygen. Bunn and Jandl (34) have recently reviewed the various experiments concerning this glycolytic intermediate. The question of whether the low levels of CO present in the blood of smokers can affect this homeostasis is presently under investigation (29, 143), and firm conclusions cannot be drawn at this time.

(c) This is an incomplete list of review articles on carbon monoxide. Fifteen others are available (see pages 6 to 10).

d Apart from its effect on hemoglobin affinity, CO appears to induce arterial hypoxemia, and this may act as an additional cause of tissue hypoxia. Ayres, et al. (14, 15) observed unexpectedly that exposure of individuals to CO sufficient to raise their levels of COHb to between 5 and 10 percent was associated with a significant fall in arterial $pO_2$. Greater fall in venous $pO_2$ was noted, but this was considered secondary to increased tissue extraction. In a recent article, Brody and Coburn (30) suggested that this COHb-induced arterial hypoxemia was due to the interaction of a number of factors. These authors noted that in the presence of veno-arterial shunts or of an imbalance in the ventilation-perfusion ratio, the shift in the oxyhemoglobin dissociation curve increased the alveolar-arterial $O_2$ gradient and resulted in arterial hypoxemia. The presence of shunts as small as 2 percent of cardiac output as well as of approximately 10 percent COHb was found to cause an increase in the gradient. Such ventilation-perfusion (V/Q) abnormalities have recently been noted even in asymptomatic smokers (see Chapter on Chronic Obstructive Bronchopulmonary Disease). The increased levels of COHb found in the blood of smokers may interact with these V/Q abnormalities to further decrease available oxygen.

Commentary (5) National Clearinghouse, Cont.

In normal individuals, coronary flow can increase to meet the increased oxygen demands of a stressed myocardium (as that under nicotine stimulation), while in individuals with severe CHD coronary flow cannot respond as readily. In such cases, myocardial oxygen extraction must be increased above the almost maximal extraction found at rest. Any interference with arterial oxygen levels or hemoglobin affinity could very well decrease available oxygen supplies below the level required for proper tissue function. That this occurs is suggested by the experiments discussed below.

(d) The studies of Ayres et al (1965, 1969) were performed in a non-steady state. These papers are discussed elsewhere in this commentary (page 148 ).

Chevalier, et al. (41) exposed 10 young nonsmokers to CO concentrations sufficient to induce COHb levels of approximately 4 percent. Taking measurements from blood specimens obtained at cardiac catheterization under resting and exercise conditions, the authors noted that the ratio of oxygen debt to oxygen uptake increased significantly under conditions of increased COHb. According to the investigators this implied that the same work was being done at a greater metabolic cost. These same authors (121, 122) had previously noted similar findings among smokers and observed that cessation of smoking was associated with a significant improvement in oxygen debt accumulation.

(e) The observations of Chevalier et al were made not on blood but on alveolar air analysis. The subjects inhaled 0.5% carbon monoxide, resulting in an indirectly measured blood value of 4% carboxyhemoglobin. There is a serious error here, since other investigators have obtained 25% to 75% carboxyhemoglobin.

More recent work by Ayres, et al. (15) has focused on the difference in response to CO exposure between 7 normals and 4 patients suffering from CHD (proven arteriographically). The induction of a COHb concentration of approximately 9 percent in the normals was followed by an increase in coronary blood flow, a decrease in hemoglobin-oxygen percent extraction and no change in myocardial oxygen consumption, coronary sinus oxygen tension, and lactate and pyruvate extraction ratios. The induction of similar COHb levels in the CHD patients was followed by no change in coronary blood flow, a decrease in the hemoglobin-oxygen extraction ratio, and no change in myocardial oxygen consumption. However, these patients did manifest a decrease in coronary sinus $pO_2$ as well as a decrease in lactate and pyruvate extraction. The latter measures indicate that the myocardium was functioning under hypoxic conditions. Because the coronary flow could not increase and because the myocardium could not extract $O_2$ from $HbO_2$ which was under the influence of CO, coronary sinus oxygen tension decreased to a point which could inactivate certain oxidative enzyme processes. Thus, the myocardial function of persons with CHD may be unable to compensate for the stresses induced by smoking.

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Commentary (5) National Clearinghouse, Cont.

(f) The comments in paragraph (d) above apply to another publication by Ayres et al (1969). These measurements were taken in a non-steady state after administering 5% carbon monoxide.

c. Although COHb levels resulting from the CO present in the atmosphere during periods of high air pollution are much lower than those due to the inhalation of cigarette smoke, these concentrations of COHb might contribute to the manifestations of CHD. Cohen, et al. (44) studied the case fatality rates for patients admitted to 35 Los Angeles area hospitals with myocardial infarction in relation to atmospheric CO pollution. The authors observed an increased MI case fatality rate in areas of increased pollution, and then only during periods of relatively increased CO pollution.

(g) The opening sentence is a poor comparison. Instead of atmospheric air and cigarette smoke a comparison between blood levels of nonsmokers and smokers would be pertinent. There is also an endogenous source of carbon monoxide.

Subsequent to a report by Cohen et al (1969), Haywood et al (1972) examined patients dying of acute myocardial infarction or diverse diseases. There was no clear-cut relationship between carbon monoxide levels and acute infarction (see page 61).

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(6) NATIONAL CLEARINGHOUSE FOR SMOKING AND HEALTH: The health consequences of smoking. A report to the Surgeon General: 1972. 21-3, 121-135, 1972.

CARBON MONOXIDE

a Because cigarette smoke contains from 2.7 to 6 percent carbon monoxide (CO), significantly higher carboxyhemoglobin (COHb) levels are found in smokers than nonsmokers (13, 20, 24, 63). COHb levels in nonsmokers are usually less than 1 percent, while those in smokers average around 4 percent and may exceed 15 percent (4, 20, 52). Heavy smokers and those who inhale show the highest carboxyhemoglobin levels (20).

(a) The blood levels of carboxyhemoglobin cited in this paragraph do not represent the values reported in the literature. For nonsmokers the level is not usually less than 1%. In the 26 investigations reported, the overall mean for 1,662 subjects was 1.45% (see pages 32 and 33). For smokers the average is not 4%. The 30 investigations reported in the literature have an overall mean of 3.76% for 2,054 subjects. Values above 15% are very rare and are probably the result of an error in the analysis (see pages 12-15).

b Haebisch (24) found that a smoker with a daily consumption of 35 to 40 cigarettes easily attains and maintains for hours an alveolar CO concentration of 50 p.p.m., which reaches or exceeds legally-established ambient air quality standards (14, 18, 23, 24).

Cohen, et al. (13) and Aronow, et al. (2) have shown that there is no significant difference in mean expired air carbon monoxide levels after patients have smoked tobacco or lettuce leaf cigarettes. Although pipe and cigar smokers in the United States are reported to have lower exposure to CO than cigarette smokers (20), CO intoxication has been reported in cigar smokers (25).

(b) The observation of Haebisch (1970) is an isolated one. It should be noted that his value of 50 ppm carbon monoxide in alveolar air is 2 to 3 times greater than that reported by Jongbloed (1939) and Ringold et al (1962) (see page 19).

c CO exerts its adverse effects on the cardiovascular system of smokers through one or more of the following mechanisms: (a) reduction of the amount of hemoglobin available for oxygen transport; (b) shift of the oxygen-hemoglobin dissociation curve to the left with consequent interference in oxygen release at the tissue level; and (c) induction of arterial hypoxemia. CO may interfere with the homeostatic mechanism by which 2,3-DPG controls the affinity of hemoglobin for oxygen (56). CO has also been implicated in experimental atherogenesis in animals (56).

(c) The list of 3 mechanisms actually represents one, which causes the formation of carboxyhemoglobin. Item (c), hypoxemia, meaning low oxygen tension, is not correct. There is low oxygen content but normal tension.

Commentary (6) National Clearinghouse, Cont.

Ayres, et al. (7) recently studied 41 patients during diagnostic cardiac catheterization, at which time they inhaled either 5 percent or .1 percent CO. Arterial and mixed venous oxygen tensions were decreased by administration of either concentration. In patients with CHD, coronary artery $O_2$ extraction decreased 7.9 percent after inhalation of .1 percent CO and 30.5 percent after inhalation of 5 percent CO. Some of the patients with CHD experienced changes in lactate and pyruvate metabolism indicative of inadequate myocardial oxygenation. The higher level of CO inhalation in this experiment is comparable to that experienced intermittently by cigarette smokers.

(d) The work of Ayres et al (1970) is based on a non-steady state and is commented upon elsewhere (see page 148).

Brewer and his colleagues (11) investigated cigarette smoking as a cause of hypoxemia in residents of Leadville, Colorado, at an altitude of 3,100 meters. The arterial $pO_2$ of 8 smokers was significantly lower ($P < .05$) than that of 12 nonsmokers, but this was reversible upon cessation of smoking. They concluded that the adverse effect of cigarette smoking on $O_2$ transport may be especially pronounced at high altitude and may restrict an individual's ability to adapt to reduced $O_2$ tensions (11, 12).

(e) The statement of the results of Brewer et al (1970, 1971) is incomplete. It should be added that the difference in oxygen tension between smokers and nonsmokers is small, amouting to 5 mm for $pO_2$. More important is the fact that the oxygen saturation for smokers is 74% and is higher than that of the nonsmoking individual (68%). The shift of the oxygen dissociation curve to the left in the blood of smokers accounts for higher oxygen saturation. Therefore, although oxygen tension is reduced, the saturation is higher for smokers. A paragraph from Brewer et al (1971) is quoted below.

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In the course of our smoking experiments we determined the CO content of the air in our 15 cu m exposure chamber (with approximately one air change/hour) and we found that the CO rose to approximately 20 ppm following the smoking of seven cigarettes in an hour. Particulate matter was 3 mg/cu m at the end of the hour. We also measured the concentrations of CO passing across the face of an observer who sat next to a subject for the ten minutes during which a cigarette was smoked. The air was sampled through a tube strapped to the observer's face, and it can be seen from FIGURE 9 that transient peaks of up to 90 ppm were measured.

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Commentary (6) National Clearinghouse, Cont.

Kjeldsen (31, 32) examined 993 industrial workers, about one-half of whom were tobacco workers. Fifty-nine cases of arteriosclerosis were documented by such clinical symptoms as angina pectoris and intermittent claudication or by a previous history of myocardial infarction. While 20.9 percent of the 934 "control" individuals were nonsmokers, only 2 (3.4 percent) of the 59 patients with arteriosclerosis were nonsmokers. A significantly higher percentage of diseased workers were heavy smokers and inhaled the smoke.

The diseased smokers had significantly higher carboxyhemoglobin and serum cholesterol levels than either smoking or nonsmoking control patients. This was true after standardizing for differences in levels of smoking between controls and diseased patients. As expected, there was a gradient in carboxyhemoglobin levels from lower levels in light smokers to higher levels in heavy smokers (table 4).

TABLE 4.—*Average values of carboxyhemoglobin and serum cholesterol in Danish smokers and nonsmokers in control group and group of patients with arteriosclerotic cardiovascular disease.*

| Smoking category | Carboxyhemoglobin (saturation percentage) controls M±S.D. | patients M±S.D. | significance | Serum cholesterol (mg/100 ml) controls M±S.D. | patients M±S.D. | significance |
|---|---|---|---|---|---|---|
| Smokers | 4.2±3.1 (738)[a] | 7.0±3.7 (57) | $p<0.001$ $t=5.52$ | 247±44 (738) | 290±33 (57) | $p<0.001$ $t=4.89$ |
| Nonsmokers | 0.4±0.9 (196) | 0.5±0.7 (2) | n.s. $t=0.16$ | 236±49 (196) | 284±56 (2) | $p<0.02$ $t=2.32$ |
| Light smokers | 2.5±2.5 (121) | 3.7±2.5 (3) | n.s. $t=0.76$ | 245±38 (121) | 279±67 (3) | n.s. $t=1.45$ |
| Moderate smokers | 4.1±3.0 (463) | 7.3±3.6 (34) | $p<0.001$ $t=4.95$ | 246±45 (463) | 286±50 (34) | $p<0.001$ $t=4.52$ |
| Heavy smokers | 5.7±3.0 (154) | 7.0±4.0 (20) | n.s. $t=1.45$ | 253±45 (154) | 298±53 (20) | $p<0.05$ $t=2.18$ |

$p$ = Probability that difference is not due to chance.
$t$ = Student's $t$ calculation.
n.s. = not significant.
[a] The number of subjects in each category is enclosed in parentheses beneath the mean (M) and standard deviation (S.D.).
SOURCE: Kjeldsen, K. (31).

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Kjeldsen also observed that the COHb levels of 8 to 19 percent seen in 40 percent of the patients with arteriosclerosis were of the same magnitude as those provoking experimental atherosclerosis and cardiac necrosis in animals.

(f) The observations of Kjeldsen (1969, 1970) have not been confirmed by others. It should be stated that Prerovska and Drdkova (1967, 1971) completed a retrospective examination of individuals who had been exposed to an environment of up to 1,000 ppm for an average duration of 10.5 years. There was no early development of arteriosclerosis.

Table 5. Carboxyhemoglobin blood levels of nonsmokers following exposure to vehicular traffic.

| Reference (Year) | Nature of subjects | No of Subjects | Carboxyhemoglobin blood levels % Before Mean | After Mean ± SD (Range) | Δ |
|---|---|---|---|---|---|
| Goldsmith, Terzaghi and Hackney (1963) | Los Angeles drivers | 1 | 1.8 | 2.5 | +10 |
| Moureu (1964) | Paris vehicular drivers | 597 | | 4.5 | |
| DeBruin, Bult and Van Haeringen (1965) | Amsterdam policemen | 10 | 1.43 | 1.74 | +0.3 |
| DeBruin, Vroege and Van Haeringen (1965) | Rotherdam policemen | 36 | 0.93 | 1.11 | +0.08 |
| Morando and Rovida (1965) | Genoa policemen | 4 | | (1.83-4.00) | |
| Alivisatos, Baza s, Alexopoulos and Verykokakis (1967) | Athens residents | 27 | 0 | | |
| Desoille (1967) | Paris garagemen | 2 | | (2.3-3.5) | |
| Srch (1967) | Prague vehicular passengers | 2 | | (2-5) | |
| Chovin (1967) | Paris policemen | 7 | | 1.25 | |
| Ramsey (1967) | Dayton parking attendent | 14 | 1.5 | 7.3 ± 3.46 | +5.8 |
| DeBruin (1967) | Amsterdam vehicular drivers | 23 | 1.9 | 2.15 | +0.25 |
| Buchwald (1969) | Alberta garage operators | 122 | | 5.0 | |
| Breysse and Bovee (1969) | Seattle fork lift drivers | 92 | | 1.2 (0-6) | |
| Gothe, Fristedt, Sundell, Kolmodin Ehrner-Samuel and Göthe (1969) | Stockholm policemen<br>Malmo policemen<br>Oreho policemen | 28<br>6<br>3 | | 1.2 ± 0.39(0.5-2.0)<br>0.8 ± 0.14(0.7-1.1)<br>0.6 ± 0.38(0.4 -1.1) | |
| Szadkowski, Mastall, Schaller and Lehnert (1970) | Nuhrenberg dustmen | 138 | | 4.04 ±282 | |
| Petrilli and Kanitz (1970) | Genoa vehicular drivers | 20 | | (1.5-3.0) | |
| Cohen, Dorion, Goldsmith, Permutt(1971) | US-Mexican border inspectors | 9 | 1.5 | 3.6 | |
| Ayres and Buehler (1970) | New York pedestrians | 1481 | | 1.0 | |
| Luderitz (1971) | Berlin policemen | 120 | | (4-7) | |
| Mean (overall for number of subjects) | | | | 2.24 (2567 subjects) | +1.12 (84 subjects |

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Since pipe and cigar smokers inhale less commonly than do cigarette smokers, their contribution to the substances in the air breathed in exposure to smoke pollutants consists of a composite of sidestream smoke and relatively unfiltered mainstream smoke which has been held in the mouth and then expelled.

The actual effluents in the mainstream and sidestream cigarette smoke have been considered by Pascasio, et al. (45) and Scassellati Sforzolini and colleagues (50, 51). These authors stated that "tar" and nicotine levels in sidestream smoke may be significantly higher than those of mainstream smoke and may be harmful to the non-smoker. Actual volume measurements were not reported, however.

Actual measurements of the contamination due to cigarette smoking have been carried out by a number of research groups. A recent, well-controlled study by Harke (24) involved the smoking of 42 cigarettes in 16 to 18 minutes using German blend cigarettes of 85 mm. length, 18 mm. filter, and smoked to a 25 mm. butt length in a room with a volume of 57 cubic meters (approximately the equivalent of a room with a 10-foot ceiling and dimensions of 12 by 14 feet). The author observed that in the absence of ventilation the atmosphere contained up to 50 p.p.m. carbon monoxide and .57 mg./m.$^3$ nicotine. With substantial ventilation, these levels fell significantly (to approximately 10 p.p.m. carbon monoxide and .10 mg./m.$^3$ nicotine). He also found that cigar smoke (9 cigars of Clear Sumatra tobacco smoked in 30 to 35 minutes) produced similar amounts of contamination while pipe smoke (8 grams of Navy type medium cut tobacco smoked as eight pipefuls in 35 to 40 minutes) produced much less. Other authors have made similar measurements. Galuskinova (20) found that 3,4-benzpyrene levels in a smoky restaurant were from 2.82 to 14.4 mg./100 m.$^3$ as compared to outside atmospheric levels of 0.23 to 0.46 mg./100 m.$^3$, although burning of food particles may have contributed to the presence of 3,4-benzpyrene in this setting. Kotin and Falk (33) have shown that sidestream cigarette smoke condensate may contain more than three times as much benzo(a)pyrene as mainstream smoke. Srch (55) observed that the smoking of 10 cigarettes to a 5 mm. butt length in an enclosed car of 2.09 m.$^3$ volume produced carbon monoxide levels up to 90 p.p.m. Lawther and Commins (34), working with a ventilated chamber, found levels of up to 20 p.p.m. of carbon monoxide after seven cigarettes were smoked in one hour; however, peaks of up to 90 p.p.m. were recorded at the seat next to the smoker. Coburn, et al. (9) recorded levels of 20 p.p.m. of carbon monoxide in a small conference room after 10 cigarettes were "burned." Harmsen and Effenberger (25) reported up to 80 p.p.m. of carbon monoxide in an enclosed 98 m.$^3$ room (approximately the equivalent of a room with a 10-foot ceiling and dimensions of 18 by 20 feet) in which 62 cigarettes had been smoked in two hours.

Another set of contaminants probably present in a tobacco smoke-polluted atmosphere are the oxides of nitrogen. These, specificially NO and $NO_2$, have been shown to be present in tobacco smoke although the type most likely to be present in the atmosphere is $NO_2$. No measurements have been reported of the amount of $NO_2$ in smoke-filled rooms. The importance of obtaining and evaluating this information is stressed by the results of Freeman and Haydon and

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their colleagues (17, 18, 19, 27, 28) and of Blair, et al. (5) who observed bronchial and pulmonary parenchymal lesions in rodents continuously exposed to low levels of $NO_2$.

Other experimenters have measured carboxyhemoglobin (COHb) levels in nonsmokers exposed to cigarette smoke pollutants. Srch (55) observed that the COHb level in two nonsmokers rose from 2 to 5 percent (that of smokers from 5 to 10 percent) when seated in the cigarette-smoke contaminated car mentioned above (exposure to 90 p.p.m.). Harke (24) reported that when seven nonsmokers were exposed for approximately 90 minutes to a "smoked" room containing 30 p.p.m. of CO there was a rise in COHb from a mean of 0.9 percent to 2.0 percent. In 11 smokers subjected to the same conditions, COHb rose from a mean of 3.3 percent to 7.5 percent. With improved ventilation of the experimental room, the COHb level decreased significantly.

The CO exposures and COHb levels reported above closely approximate the results obtained following experimental chamber exposure of humans to various levels of CO. The uptake of CO by the person depends on, among other parameters: CO concentration, previous COHb level, the level of activity, and the person's state of health. Equilibrium between CO concentration in the lung and in the blood requires over 12 hours exposure. However, as may be noted in table 1, reproduced from Stewart, et al. (56) and derived from measures of COHb in young sedentary males who were not smoking, over half of the equilibrium COHb level is reached within three to four hours of the onset of exposure. The equilibrium value associated with 100 p.p.m. is approximately 14 to 15 percent COHb. Exposure to 100 p.p.m. in the nonsmoker can lead to 3.0 percent of COHb within 60 minutes and 6.0 percent in two hours (16). Of equal significance is that COHb has a half-life of at least three to four hours in the body. As shown in table 1, the COHb level fell only to 2.7 percent in the two hours following cessation of exposure to 50 p.p.m. from the end exposure level of 3.7 percent. This lengthy half-life extends the period of effect of exposure to CO and provides for a buildup of COHb concentration from fresh exposures.

TABLE 1.—*Percent of COHb during and following exposure to 50 p.p.m. of CO.*

| Time during exposure | Mean | Range | Number of subjects |
|---|---|---|---|
| Preexposure | 0.7 | 0.4–1.5 | 11 |
| 30 minutes | 1.3 | 1.3 | 3 |
| 1 hour | 2.1 | 1.9–2.7 | 11 |
| 3 hours | 3.8 | 3.6–4.2 | 10 |
| 6 hours | 5.1 | 4.9–5.5 | 5 |
| 8 hours | 5.9 | 5.4–6.2 | 5 |
| 12 hours | 7.0 | 6.5–7.9 | 3 |
| 15 ½ hours | 7.6 | 7.2–8.2 | 3 |
| 22 hours | 8.5 | 8.1–8.7 | 3 |
| 24 hours | 7.9 | 7.6–8.2 | 3 |
| Time without exposure after 1 hour of exposure | | | |
| 30 minutes | 1.8 | 1.8 | 3 |
| 1 hour | 1.7 | 1.6–1.8 | 3 |
| 2 hours | 1.5 | 1.4–1.5 | 3 |
| 5 hours | 1.1 | 1.0–1.1 | 2 |

Commentary (6) National Clearinghouse, Cont.

| | | | |
|---|---|---|---|
| Time without exposure after 3 hours of exposure | | | |
| 30 minutes | 3.7 | 3.4–3.9 | 3 |
| 1 hour | 3.3 | 2.7–3.8 | 3 |
| 2 hours | 2.7 | 2.3–3.0 | 3 |
| Time without exposure after 8 hours of exposure | | | |
| 30 minutes | 5.6 | 5.1–5.9 | 3 |
| 1 hour | 5.1 | 4.8–5.4 | 3 |
| 1 ½ hours | 4.0 | — | — |
| 11 hours | 1.5 | 1.4–1.7 | 3 |
| Time without exposure after 24 hours of exposure | | | |
| 30 minutes | 7.5 | 7.2–7.8 | 3 |
| 1 hour | 6.7 | 6.4–7.1 | 3 |
| 2 hours | 5.8 | 5.6–6.2 | 3 |

(g) This section includes an incomplete citation of work by the various investigators. For ins tance, Harke's conclusion that "it is unlikely to find non-smokers in a room absorbing a significant amount of cigarette smoke" is not mentioned at all. The blood levels that show low absoprtion are mentioned two paragraphs later. The passive smoker had a blood level of 2% carboxyhemoglobin, an increase of 1.1% over the control level (see page 25).

(h) Srch (1967) not only s moked "in an enclosed car" but also had the motor running in a closed garage. The high levels of carbon monoxide arise largely from automobile exhaust and this is not stated in the quotation (see page 36).

(i) Lowther and Cummins (1970) worked with a ventilated chamber. Examination of the original article reveals that the chamber is 15 cu m, with approximately 1 air change per hour. The high values for carbon monoxide in the air are understandable (see paragraph from article).

Data from 2 representative oxygen tensions are shown in Figure 5 and Table 4. Although there is overlap, the mean saturation values of the normal smokers and the polycythemic smokers are significantly higher than that of non-smoking normals at one of the two oxygen tensions (Table 5). This means that, on the average, the oxygen dissociation curve of smokers in Leadville is left-shifted compared to non-smokers. There was no significant difference between the position of the curve in normal smokers and polycythemic smokers at either oxygen tension.

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THE EFFECTS OF LOW LEVELS OF
CARBON MONOXIDE ON HUMAN HEALTH

The data on the effect of low levels of carbon monoxide on human psychological and physiological function have been summarized in two recent publications (8, 53).

There is presently much discussion as to the physiologic and psychophysiologic effects of exposure to levels of CO approximating 50 to 100 p.p.m. Beard and Grandstaff (4) observed that exposure to 50 p.p.m. of CO for from 27 to 90 minutes altered auditory discrimination, visual acuity, and the ability to distinguish relative brightness. McFarland (39) observed that COHb levels of 4 to 5 percent caused visual threshold impairment. Ray and Rockwell (48), reporting on a study of the driving ability of three subjects under varying CO exposure, observed that the presence of 10 percent COHb was associated with increased response time for taillight discrimination and increased variance in distance estimation. Schulte (52) observed that increased errors in cognitive and choice discrimination tests were manifest at levels of COHb as low as 3 percent. Chevalier, et al. (7) have also observed that levels of 4 percent COHb in nonsmokers are associated with an increase in oxygen debt formation with exercise similar to that seen in smokers.

On the other hand, other investigators utilizing complex psychomotor tasks in men and monkeys have observed no decrement in function upon exposures to CO at 50 to 250 p.p.m. (2, 3, 23, 41, 56).

(j) The investigations that concentration of 50 to 250 ppm carbon monoxide does not influence the central nervous system are not described in detail. There are many other reports which are also negative (see Pages 88-90).

Animals exposed to low levels of CO (50 to 100 p.p.m.) continuously for weeks have shown varying degrees of cardiac and cerebral damage similar to that produced by hypoxia (21, 47, 57).

Finally, the possible effects of exposure to 50-100 p.p.m. CO on patients with coronary heart disease (CHD) were investigated by Ayres, et al. (1) who observed a decrease in arterial and mixed venous oxygen tensions with COHb saturations of 5 percent. Certain patients with CHD developed altered lactate and pyruvate metabolism with COHb levels of 5 to 10 percent suggesting myocardial hypoxia.

(k) The cited work of Ayres et al (1970) was performed in a non-steady state with inhalation of 5% carbon monoxide. The validity of these observations is discussed elsewhere in this commentary (see page 148).

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¶ The evidence concerning the effect of low levels of carbon monoxide has recently been reviewed and evaluated by the National Air Quality Criteria Committee of the National Air Pollution Control Administration (55). The following is taken from the published conclusions of the Advisory Committee (also see table 2):

> "Experimental exposure of nonsmokers to 58 mg/m³ (50 ppm) for 90 minutes has been associated with impairment in time-interval discrimination.... This exposure will produce an increase of about 2 percent COHb in the blood. This same increase in blood COHb will occur with continuous exposure to 12 to 17 mg/m³ (10 to 15 ppm) for 8 or more hours....
>
> "Experimental exposure to CO concentrations sufficient to produce blood COHb levels of about 5 percent (a level producible by exposure to about 35 mg/m³ for 8 or more hours) has provided in some instances evidence of impaired performance on certain other psychomotor tests, and an impairment in visual discrimination....
>
> "Experimental exposure to CO concentrations sufficient to produce blood COHb levels above 5 percent (a level producible by exposure to 35 mg/m³ or more for 8 or more hours) has provided evidence of physiologic stress in patients with heart disease...."

The levels of carbon monoxide found to be present in "smoked" rooms (20 to 80 p.p.m.) are similar to the levels (30 to 50 p.p.m.) which the Advisory Committee has concluded are associated with adverse health effects:

> "An exposure of 8 or more hours to a carbon monoxide concentration of 12 to 17 mg/m³ (10 to 15 ppm) will produce a blood carboxyhemoglobin level of 2.0 to 2.5 percent in nonsmokers. This level of blood carboxyhemoglobin has been associated with adverse health effects as manifested by impaired time interval discrimination. Evidence also indicates that an exposure of 8 or more hours to a CO concentration of 35 mg/m³ (30 ppm) will produce blood carboxyhemoglobin levels of about 5 percent in nonsmokers. Adverse health effects as manifested by impaired performance on certain other psychomotor tests have been associated with this blood carboxyhemoglobin level, and above this level there is evidence of physiologic stress in patients with heart disease."

These levels of CO are also similar to that set as the time-weighted occupational Threshold Limit Value of 50 p.p.m. for a 40-hour week (five 8-hour days) which has been in effect in the United States for the past several years (15). A further reduction in this limit to 25 p.p.m. is now under consideration. These levels of CO exceed those recently set by the Environmental Protection Agency as the national primary and secondary ambient air quality standards for CO (14). These standards are:

(a) 10 milligrams per cubic meter (9 p.p.m.)—maximum 8-hours concentration not to be exceeded more than once per year.

(b) 40 milligrams per cubic meter (35 p.p.m.)—maximum 1-hour concentration not to be exceeded more than once per year.

TABLE 2.—*Effects of carbon monoxide.*

| Environmental conditions | Effect | Comment |
|---|---|---|
| 58 mg./m.$^3$ (50 p.p.m.) for 90 minutes | Impairment of time-interval discrimination in non-smokers. | Blood COHb levels not available, but anticipated to be about 2.5 percent. Similar blood COHb levels expected from exposure to 10 to 17 mg./m.$^3$ (10 to 15 p.p.m.) for 8 or more hours. |
| 115 mg./m.$^3$ (100 p.p.m.) intermittently through a facial mask | Impairment in performance of some psychomotor tests at a COHb level of 5 percent. | Similar results may have been observed at lower COHb levels, but blood measurements were not accurate. |
| High concentrations of CO were administered for 30 to 120 seconds, and then 10 minutes was allowed for washout of alveolar CO before blood COHb was measured. | Exposure sufficient to produce blood COHb levels above 5 percent has been shown to place a physiologic stress on patients with heart disease. | Data rely on COHb levels produced rapidly after short exposure to high levels of CO; this is not necessarily comparable to exposure over a longer time period or under equilibrium conditions. |

SOURCE: Adapted from U.S. Public Health Service. Air Quality Criteria for Carbon Monoxide. Washington, D.C., U.S. Department of Health, Education, and Welfare (53).

(1) The remainder of this section quotes the decision by the National Air Pollution Control Administration, which was drafted mainly for industrial exposures lasting 8 hours. The criteria used by this agency do not apply to brief exposures to cigarette smoke.

## ALLERGIC AND IRRITATIVE REACTIONS TO CIGARETTE SMOKE AMONG NONSMOKERS

(A more detailed discussion of this subject is presented in the Allergy chapter of this report.)

Several investigators have reported on the discomfort and symptoms experienced by both allergic and nonallergic individuals upon exposure to tobacco smoke. Johansson and Ronge (31, 32) in 1965 and 1966 have observed that the acute irritation experienced by nonsmokers in the presence of tobacco smoke is maximal in warm, dry air and that nonsmokers experience more nasal irritation than ocular irritation as compared with smokers exposed to similar amounts of smoke in the atmosphere. Speer (54) studied the reactions of 441 nonsmokers divided into two groups, one composed of individuals with a history of allergic reactions and the other of individuals without such a history. The allergic group underwent skin testing for the presence of sensitivity to tobacco extract while the "nonallergic" group was determined solely by questionnaire concerning subjective allergic responses. Approximately 70 percent of both groups experienced eye irritation while other symptoms differed in their frequency from group to group (nasal symptoms:

allergic 67 percent, "nonallergic" 29 percent; headache: allergic 46 percent, "nonallergic" 31 percent; cough: allergic 46 percent, "nonallergic" 25 percent; and wheezing: allergic 22 percent, "nonallergic" 4 percent). Thus, a significant proportion of nonsmoking individuals report discomfort and respiratory symptoms on exposure to tobacco smoke.

Other authors have attempted to separate out those patients who may have specific allergies to smoke. Zussman (*61*) found that in a random series of 200 atopic patients 16 percent were clinically sensitive to tobacco smoke, and that a majority of these were aided by desensitization therapy. In an earlier study, Pipes (*46*) observed that 13 percent of 229 patients with respiratory allergy showed positive skin tests to tobacco smoke. Savel (*49*) has recently reported on eight nonsmokers observed to be clinically hypersensitive to tobacco smoke. After *in vitro* incubation of their lymphocytes with cigarette smoke, increased incorporation of tritiated thymidine was recorded; similar exposure of the lymphocytes of those not sensitive resulted in depression of tritiated thymidine uptake.

Luquette, et al. (*39*) have recently reported on the immediate effects of exposure to cigarette smoke in school-age children. They observed that heart rate and blood pressure rose with such exposure, although questions remain about the adequacy of their controls and the manner in which the experimental situation may have excited the subjects. Finally, Cameron, et al. (*6*) observed that acute respiratory illnesses were more frequent among children from homes in which the parents smoked than among children of nonsmoking parents. The meaning of these results is uncertain since smoking by the children was not considered and the level of exposure to cigarette smoke in their homes was not measured. Shy, et al. (*53*) in a study of second grade Chattanooga school children failed to demonstrate a relationship between parental smoking habits and the respiratory illness rates of their children.

(m) This section on allergic reactions refers to components of cigarette smoke other than carbon monoxide. There is no case of reported allergy to carbon monoxide.

THE KNOWN HARMFUL EFFECTS OF THE PASSIVE INHALATION OF CIGARETTE SMOKE IN ANIMALS

A number of investigators have studied the effects of the passive inhalation of high concentrations of cigarette smoke on the pulmonary parenchyma and tracheobronchial tree of animals. The results of these investigations are listed in detail in the recent report to Congress, "The Health Consequences of Smoking," (*59*) in table 9 of the Bronchopulmonary chapter, and table 16 of the Cancer chapter.

The pathologic changes observed in the respiratory tract of the animals included parenchymal disruption, bronchitis, tracheobronchial epithelial dysplasia and metaplasia, and pulmonary adenomatous tumor formation. Leuchtenberger, et al. (36) exposed 151 mice to the smoke of from 25 to 1,526 cigarettes over a period of 1 to 23 months and observed that 20 percent of the animals developed severe bronchitis with atypism. Working with 30 control rabbits exposed to up to 20 cigarettes per day for two to five years, Holland, et al. (30) observed increased focal and generalized hyperplasia of the bronchial epithelium and generalized emphysema in the exposed rabbits. Hernandez, et al. (29) observed significantly more pulmonary parenchymal disruption in adult greyhound dogs exposed to cigarette smoke 10 times per week for approximately one year than in nonexposed control animals.

Lorenz, et al. (38) observed no increase in respiratory tract tumor formation above that seen in controls in 97 Strain A mice exposed to cigarette smoke for up to 693 hours. Essenberg (15), however, exposed Strain A mice to cigarette smoke for 12 hours a day for up to one year and observed significantly more papillary adenocarcinomas in the exposed than in the control group. An increased percentage of hybrid mice were found by Mühlbock (42) to have alveolar carcinomas among the experimental group exposed to smoke for two hours a day for up to 684 days when compared with a nonexposed group. Similarly, Guerin (22) observed that 5.1 percent of rats exposed to cigarette smoke for 45 minutes a day for two to six months showed pulmonary tumors compared to 2.4 percent of the control mice.

Leuchtenberger, et al. (37), working with 400 female $CF_1$ mice, observed only a slight increase in the presence of pulmonary adenomatous tumors among those exposed to cigarette smoke compared with those in the control group. The authors commented that the presence of tumors showed an age relationship independent of smoking exposure. Otto (43) found that 11 percent of a group of albino mice exposed to 12 cigarettes a day for up to 24 months showed pulmonary adenomas as compared with five percent of the control non-exposed group. Dontenwill and Wiebecke (12) found that increasing the exposure of golden hamsters to up to four cigarettes a day for up to two years was associated with an increasing percentage of animals showing desquamative metaplasia and bronchial papillary metaplasia. Harris and Negroni (26) exposed 200 C57BL mice to cigarette smoke for 20 minutes a day every other day for life and found eight adenocarcinomas as compared to none in the control group.

Because the damage observed in these experiments was seen after prolonged exposure to high concentrations of cigarette smoke, and because the comparability of animal exposure to smoke with that of human exposure in smoke-filled rooms is unknown, it is presently impossible to be certain from animal experimentation about the extent of the damage that may occur during long-term intermittent exposure to lower concentrations.

## SUMMARY

1. An atmosphere contaminated with tobacco smoke can contribute to the discomfort of many individuals.

2. The level of carbon monoxide attained in experiments using rooms filled with tobacco smoke has been shown to equal, and at times to exceed, the legal limits for maximum air pollution permitted for ambient air quality in several localities and can also exceed the occupational Threshold Limit Value for a normal work period presently in effect for the United States as a whole. The presence of such levels indicates that the effect of exposure to carbon monoxide may on occasion, depending upon the length of exposure, be sufficient to be harmful to the health of an exposed person. This would be particularly significant for people who are already suffering from chronic bronchopulmonary disease and coronary heart disease.

3. Other components of tobacco smoke, such as particulate matter and the oxides of nitrogen, have been shown in various concentrations to adversely affect animal pulmonary and cardiac structure and function. The extent of the contributions of these substances to illness in humans exposed to the concentrations present in an atmosphere contaminated with tobacco smoke is not presently known.

(n) The experiments on animals were not controlled and there is no reported concentration of carbon monoxide. It is not possible to relate the observations on animals to humans unless the concentration of cigarette smoke is known.

(7) ABELSON P H : A damaging source of air pollution. Science 158: 1527, 1967.

> One of the toxic products of the automobile is carbon monoxide. Exposure for 1 hour to a concentration of this gas of 120 parts per million causes inactivation of about 5 percent of the body's hemoglobin and commonly leads to dizziness, headache, and lassitude. Concentrations of carbon monoxide as high as 100 ppm often occur in garages, in tunnels, and behind automobiles. Such concentrations are tiny in comparison with those (42,000 ppm) found in cigarette smoke. The smoker survives because most of the time he breathes air not so heavily polluted. However, in a poorly ventilated, smoke-filled room, concentrations of carbon monoxide can easily reach several hundred parts per million, thus exposing smokers and nonsmokers present to a toxic hazard.

In this article, the comparison of concentration of carbon monoxide is as follows: 100 ppm for garages and tunnels and 42,000 ppm in cigarette smoke. The latter represents 4.2 carbon monoxide in pure cigarette smoke. This concentration is not inhaled continuously, but is diluted by air in the lungs at the time of inhalation of cigarette smoke. After exhalation, atmospheric air enters to replace the cigarette smoke. Ringold et al. (1962) analyzed the expired air to determine the integrated concentration of carbon monoxide therein: that of heavy smokers had a concentration of 16.4 ppm, light smokers 7.7 ppm, and nonsmokers 0.08 ppm (see page 19).

(8) ANON : Carbon monoxide. Am Industr Hyg Ass J 26: 431-4, 1965.

> The blood of cigarette smokers will contain from 2% to 10% carboxyhemoglobin and nonexposed adults will show a normal average background of 1% carboxyhemoglobin.[1]

The blood volumes for smokers are overestimated and those for nonsmokers underestimated. The overall mean value reported in 30 investigations is 3.76% for smokers (see page 12). The overall mean value recorded in 26 investigations is 1.45% for nonsmokers.

1005051206

(9) ANON: Carbon monoxide poisoning - a timely warning. New England J Med 278: 849-50, 1968.

The cigarette is another producer of carbon monoxide. Heavy cigarette smokers may have as much as 10 per cent carbon monoxide hemoglobin in their blood. Such levels may not be sufficient to cause impairment at sea level but will be enough to produce changes at altitudes of 8000 to 10,000 feet. A recent article has demonstrated behavioral impairment associated with small doses of carbon monoxide[3] – levels of exposure in the range accepted as tolerable in industry. The results indicate that impairment of cerebral function can occur at extremely low levels (50 to 250 ppm) during exposures of half an hour to two and a half hours. Further support for central-nervous-system effects comes from the observation that low levels of carbon monoxide hemoglobin can significantly raise the threshold of light sensitivity of the eye.[4]

That heavy cigarette smoking may cause as much as 10% carboxyhemoglobin in the blood is rare. Barach et al (1941) measured the peak levels in the blood of 18 subjects who smoked 20 cigarettes daily and noted a mean level of 5.7%, with a range of 2.2% to 12.3%. Fabre et al (1951), in a group of 5 subjects smoking 24 cigarettes, reported a mean level of 4.85%, which represented an increase of 2.7% over the level prior to smoking (see page 21).

1005051207

(10) ANON : Warning: Cigarettes are dangerous to your health. American Cancer Society. Med Bull Montgomery County Med Soc 24: 45-7, 1968.

> Some of these carcinogens may be as simple carbon monoxide – CO – one of the standard by-products of automobile exhaust. Colorless and odorless, this compound of carbon and oxygen is fatal when as little as one-tenth of one percent is breathed in continuously; in minute quantities and repeated doses, it can also be a slow cause of death as a producer of cancer.

Carbon monoxide is not a carcinogen. Carbon monoxide has been tested in mice with tumors induced by chemicals. Carbon monoxide did not influence the rate of tumor growth.

(11) ANON: World action on smoking. Brit Med J 4: 65, 1971

> Carbon monoxide may be a toxic ingredient of tobacco smoke that deserves more attention than it has received. P. Astrup[1] has recently reported that exposure of rabbits to low concentrations of carbon monoxide can lead to production of atheroma. The carboxyhaemoglobin content of the blood of cigarette smokers may exceed 10%, and Astrup believes that this may be more important than nicotine in relation to coronary disease. Further research on this aspect is certainly needed.

There are two statements that should be modified. Astrup's experiments were performed on rabbits fed with cholesterol and their blood levels showed 15% carboxyhemoglobin (see page 69). That the blood levels of smokers may exceed 10% is a rarity (see pages 20-21).

(12) ANON : Cigarette smoking and carbon monoxide. Med Letter Drug Ther 13: 91-2, 1971.

In addition to nicotine, tars, and other chemical compounds, carbon monoxide has been incriminated as a pathogenic factor in cigarette smoke. Recent studies have suggested that heavy cigarette smoking (more than 20 cigarettes a day) may result in an intake of carbon monoxide that could impair the performance of the smoker in driving a car or piloting an airplane.

The average concentration of carbon monoxide in cigarette smoke is about 20,000 parts per million or about 400 ppm in the inhaled mixture of smoke and air (J. R. Goldsmith and S. A. Landaw, Science, 162:1352, 1968). The additive effects of carbon-monoxide-polluted air must also be taken into account. In Los Angeles, where high atmospheric carbon monoxide levels have caused concern, the concentration in the air during a four-year study ranged from 7.3 to 20.2 ppm (A. C. Hexter and J. R. Goldsmith, Science, 172:265, 1971).

The reference to the paper by Goldsmith and Landaw (1968) regarding 400 ppm of an inhaled mixture of smoke and air appears in this article. Since Goldsmith and Landaw cite no reference, it is not possible to challenge their source. Jongbloed (1939) analyzed the alveolar air and noted a peak level of 31.5 ppm carbon monoxide. Ringold et al (1962) analyzed the expired air after a 20-second breath-holding period and noted a level of 16.4 ppm for heavy smokers (see page 19).

1005051210

(13) ARONOW W S, KAPLAN M A and JACOB D : Tobacco: A precipitating factor in angina pectoris. Ann Int Med 69: 529-36, 1938.

(14) ARONOW W S, DENDINGER J and ROKAW S N : Heart rate and carbon monoxide level after smoking high-, low-, and non-nicotine cigarettes. A study in male patients with angina pectoris. Ann Int Med 74: 697-702, 1971.

(15) ARONOW W S and ROKAW S N : Nonnicotine cigarettes. Effects in angina pectoris. Circulation 44: 782-8, 1971.

(16) ARONOW W S, HARRIS C N, ISBELL M W, ROKAW S N and IMPARATO B : Effect of freeway travel on angina pectoris. Ann Int Med 77: 669-76, 1972.

These four publications from Aronow's group have been widely quoted as supporting the theory that carbon monoxide causes coronary heart disease. It should be noted that the investigation concerns carbon monoxide contained in cigarette smoke and in vehicular exhaust. There is no comparative study using carbon monoxide in air to ascertain that the results are due to carbon monoxide contained in vehicular exhaust or cigarette smoke.

Not all four reports include blood analysis for carboxyhemoglobin. In the first, none is recorded, in the second, blood was analysed, in the third, alveolar-expired air was used, and in the fourth, both blood and air had analysis.

SIEGEL P V and MOHLER S R : Medical factors in U. S. general aviation accidents. Aerospace Med 40: 180-4, 1969. A 184

STEVENS P J : The search for the cause of an accident. Proc Roy Soc Med 61: 1076-9, 1968. A 185

VOROSMARTI J Jr, BRADLEY M E, LINAWEAVER P G, KLECKNER J C and ARMSTRONG F W : Helium-oxygen saturation diving: I. Hematologic, lactic acid dehydrogenase and carbon monoxide-carboxyhemoglobin studies. Aerospace Med 41: 1347-53, 1970. A 186

(19) AYRES S M: Roles of carbon monoxide and nicotine in circulatory effects of cigarette smoke. JAMA 219: 520, 1972.

## Roles of Carbon Monoxide and Nicotine in Circulatory Effects of Cigarett Smoke

**Q** *I would like information about the specific factors that cause cigarette smoking to have an adverse effect on the cardiovascular system. Is it only nicotine that is involved, or can carbon monoxide and its effect on carboxyhemoglobin levels be implicated?*

Austin H Simons, MD
New Rochelle, NY

**A** Until recently, the pharmacology of tobacco smoke was thought to be essentially that of nicotine, and most early articles on the toxicity of cigarette smoke emphasized nicotine to the exclusion of other considerations. It seems likely, however, that the 3% to 4% of carbon monoxide found in cigarette smoke may play an important role intensifying the recognized cardiovascular toxicity of nicotine. Carboxyhemoglobin levels as low as 3% to 4% may increase the oxygen debt of exercise[1] and we have shown that levels of carboxyhemoglobin between five and ten percent may produce abnormal myocardial metabolism in patients with coronary artery disease. Smokers generally have 3% to 7% of their hemoglobin saturated with carbon monoxide. The whole subject has been recently reviewed in a New York Academy of Science monograph on carbon monoxide[2] and in the progress reports from the Surgeon General's office on cigarette smoking and health.

The toxicity of tobacco smoke appears to derive from both its nicotine and carbon monoxide content. Nicotine increases cardiac work by increasing heart rate and blood pressure. Carbon monoxide interferes with the ability of the heart to extract oxygen from the perfusing blood. The combination of increased oxygen requirements and decreased oxygen availability may well lead to myocardial ischemia, particularly in patients with coronary artery disease.

Stephen M Ayres, MD
St. Vincent's Hospital
and Medical Center
New York

1. Chevalier RB, Krumholz RA, Ross JC: Effects of carbon monoxide inhalation on the cardiopulmonary responses of non-smokers to exercise. *J Lab Clin Med* 62:167, 1963.
2. Coburn RF (ed): *Biological Effects of Carbon Monoxide*. New York, New York Academy of Science, 1970.

1005051213

Commentary (19) Ayres Cont.

The author cites Chevalier et al, a reference which appeared in 1963 as an abstract and does not contain results of blood levels of carboxyhemoglobin. In a subsequent paper (JAMA 198: 1061-64, 1966) Chevalier et al reported the results of inhaling 0.15% carbon monoxide, which caused a carboxyhemoglobin level of 3.95%. This value is lower than results of others, who obtained levels of 10% to 15% of carboxyhemoglobin. Chevalier et al used an indirect technique based on analysis of alveolar air, so that it is possible that by this technique they underestimated the true value if blood analysis was used. The technique employed was as follows:

> For determination of COHb levels in the blood, the relationship of Haldane and Smith was used.[6] Forster and co-workers,[3] adapted the Haldane relationship for determination of COHb by using a modification of Sjöstrand[7] in which alveolar gas is equilibrated with pulmonary blood and the equilibrated capillary carbon monoxide tension is measured directly in a sample of expired alveolar gas. This method, as utilized by Forster and co-workers,[3] gave results in the same range as those found by analysis of whole venous blood for COHb. Our technique for equilibration of capillary carbon monoxide tension was similar to that described above with certain modifications.[4,5] The Haldane relation states the following (atm signifies atmosphere):
>
> $$COHb/O_2Hb = 210\ CO \text{ pressure in atm}/O_2 \text{ pressure in atm}$$
>
> $$\%\ COHb = \frac{100}{\dfrac{O_2 \text{ pressure in atm}}{210\ CO \text{ pressure in atm}} + 1}$$
>
> When there is little reduced hemoglobin present, 210 is the M fraction established by Haldane. This technique for determination of COHb showed a satisfactory relationship when compared with the COHb level as determined spectrophotometrically on the venous blood of nine control subjects.

1005051214

ROBIN E, RAVENS K G and BING R J : Die Wirkung von Alkohol, Nikotin und Zigarettenrauchen auf das Herz. (The effect of alcohol, nicotine and cigarette smoking on the heart.) Deutsch Med J 20: 19-29, 1969. 327

SCHIEVELBEIN H and EBERHARDT R : Cardiovascular actions of nicotine and smoking. J Na Canc Ins 48: 1785-94, 1972. 328

SZÖLLÖSI E, MEDVE F and JENEY E : Angaben zur Wirkung des niedrigen Kohlenmonoxyd-Gehaltes in der Luft auf den Menschen. (Data on the effect of a low carbon monoxide content in the air on man.) Z Arbeitsmed 20: 263-8, 1970. 329

TIBBLIN G : Hjärtinfarkt och rokning. (Harmful clinical effects of smoking. Myocardial infarct and smoking.) Soc Med Tid 2: 65-7, 1971. 330

WIKTOR Z : Sprawozdanie z posiedzen naukowych wroclawskiego oddzialu towarzystwa internistow polskich w r, 1952. (Report on the scientific session of the Wroclaw branch of the Polish Society of Internal Medicine in 1952. Pol Arch Med Wewn 24: 596-7, 1954. 331

ZEH E : (Heart function disorders after carbon monoxide or E605 poisoning. Med Welt 1: 339-40, 1960. 332

Commentary (20) Banyai, Cont.

motor vehicles discharge 66 million tons of carbon monoxide annually. No wonder that in all major cities at busy intersections during hours of peak traffic the concentration of this harmful gas is much higher than the maximum allowable concentration, victimizing drivers, pedestrians and traffic policemen. Carbon monoxide in cigarette smoke is an incomplete combustion product even though the temperature at the burning zone of the cigarette is 884°C (1,623.2°F) while air is being drawn through the cigarette. Carboxyhemoglobin level of the blood is 4-6 percent in moderate smokers and up to 12 percent in heavy smokers. Its potential hazard can be estimated by adding these figures to those pertaining to motor vehicle drivers.

Andrew L. Banyai, M.D.

a. If hyperventilation increases carbon monoxide uptake, it will also hasten its removal from the blood. One technique for promoting the elimination of carbon monoxide in acute poisoning is to increase depth of respiration by having the patient inhale 5% carbon dioxide in oxygen.

b. In urban populations, the carboxyhemoglobin level in the blood is greater than 0.62% to 1.24%. In the 26 investigations reported in the literature the overall mean for 1,662 subjects was 1.45%. Residents of London, Los Angeles and Milan show the following mean levels respectively: 3.5%, 2.3% and 2.8%. These values represent a significant contribution by carbon monoxide to pollution in the atmosphere (see pages 32 and 33).

c. The effects listed in 15 lines are derived from toxic concentrations of carboxyhemoglobin ranging from 50% to 100%. The phrase "toxic concentration" appear only in the first sentence but applies to the next 3 sentences.

d. The experiments in rabbits fed with cholesterol are not supported by those in dogs reported by De Bias et al (1972). Chronic exposure to carbon monoxide does not exaggerate myocardial ischemia (see page 62).

e. There is no published report that psychomotor and cognitive areas in the brain can be influenced by levels of carboxyhemoglobin between 2% and 5%. More accurate statistics would be between 5% and 20% (see pages 88-89).

f. The effect of carbon monoxide on alveolar macrophages of experimental animals is encountered with levels of 0.5% to 2% in inspired air. Smokers have a level of carbon monoxide of 7 to 12 ppm in expired air, which is 1000 less than the concentration used in experiments on animals.

g. The levels of 4% to 6% carboxyhemoglobin in moderate smokers and 12% in heavy smokers is not supported by values stated in the literature. Balbo et al (1966) reported a mean level of 2.8% for 7 smokers, each consuming 30 cigarettes daily. Rouch et al (1971) reported a mean of 4.25% for 15 smokers using more than 10 cigarettes daily (see page 15).

1005051216

(21) BARTLETT D Jr: Pathophysiology of exposure to low concentrations of carbon monoxide. <u>Arch Environ Health</u> 16: 719-27, 1968.

"Regular cigarette smokers have repeatedly been shown to have COHb concentrations in the 5% to 10% range.[6,7] Smokers of pipes and cigars have COHb levels that are somewhat lower than those of cigarette smokers, but higher than those of nonsmokers. These findings have led to the widespread error of supposing that smokers may be more susceptible to environmental CO than nonsmokers. Carbon monoxide from cigarette smoke and CO in the ambient air are not additive in their biologic effect. Carbon monoxide is absorbed only when the Pco in the ambient air exceeds that in the pulmonary capillary blood. Thus, persons with COHb levels of 5% from smoking do not absorb further CO from the environment unless the ambient CO concentration is 30 ppm or more; on the contrary, they excrete CO at a rate roughly proportional to the Pco gradient between their blood and the ambient air. This suggests that smokers may be among the least susceptible of persons exposed to low atmospheric concentrations of CO, since their COHb concentrations are not increased by the exposure. This conclusion is modified, however, by the fact that smokers' CO excretion between cigarettes is slower in a CO-polluted environment than in pure air. Thus, their long-term average COHb concentrations are slightly higher in the presence of environmental CO than in its absence.

.... The death rate from coronary heart disease is considerably higher for smokers than for nonsmokers.[27] The rate for exsmokers is no higher than for persons who have never smoked. This pattern implies that the smoking effect is completely reversible when an individual stops smoking. Thus, smoking must cause myocardial hypoxia by some acute, reversible process, probably unrelated to the formation of hard, irreversible, atherosclerotic lesions. Carbon monoxide fits this epidemiologic pattern quite well, but nicotine or other components of cigarette smoke may be responsible, and the question remains unsolved."

The two paragraphs quoted from this article emphasize two points: (1) Carbon monoxide from cigarette smoke and that in the ambient air are not additive in their biologic effect; and (2) the effect of smoking on coronary heart disease is reversible. These two points were missed in the main text of this review and their conception properly belongs to Bartlett.

1005051217

(22) CAMM A J : The effects of smoking. Guy Hosp Gaz 81: 185-203, 1967.

Some three hundred different constituents of tobacco smoke have been identified, many of them in infinitessimally small quantities. The two substances present in the greatest amounts are carbon monoxide and nicotine. Although carbon monoxide is found in high proportions in the mainstream smoke of a cigarette, it is seldom found in high proportions combined with haemoglobin in the blood. The percentage of carboxy-haemoglobin rarely rises above five per cent unless cigarettes are "chain-smoked" in which case it may rise to ten per cent. This is not sufficient to be of clinical significance.

This review article includes a section on "contents of tobacco smoke". The paragraph quoted summarizes the present status of carboxyhemoglobin levels in cigarette smokers, concluding with the statement: "This is not sufficient to be of clinical significance".

(23) CONROY J P : Smoking and the anesthetic risk. Anest Anal 48: 388-400, 1969.

> It takes 24 hours in a carbon monoxide free atmosphere to reduce a carboxyhemoglobin of 18 to 5 percent.[31] Is it extravagant to demand 72 smoking-free hours before anesthesia?

The 24 hours required to reduce carboxyhemoglobin in the blood from 18% does not apply to the time required to reduce from 5% the blood level of carboxyhemoglobin in cigarette smokers. In the literature, 4 to 12 hours after smoking, the mean blood level for 2,054 habitual smokers is 3.76%. This value, compared with the level for nonsmokers, represents an increase of 2.19% attributed to smoking. Because of endogenous and exogenous sources of carbon monoxide other than cigarette smoking, it is not possible to reduce the carboxyhemoglobin level below 1.5% (see pages 12-13). An answer to the question raised by Conroy should be as follows: Waiting 72 hours is unreasonable; 4 to 12 hours would be sufficient.

1005051219

(24) CURPHEY T J : Carboxyhemoglobin in relation to smoking. Nat Cancer Inst Monogr 28: 231-5, 1968.

This is an excellent discussion of the significance of the carboxyhemoglobin level in relation to smoking. The entire article is reproduced.

## Carboxyhemoglobin in Relation to Smoking

THEODORE J. CURPHEY, *M.D.,*[1] *Chief Medical Examiner—Coroner, Los Angeles County, Los Angeles, California 90012*

THE main thrust of the Conference and the tenor of discussion in the general sessions and in this workshop have been to review and analyze the various agents in tobacco smoke with regard to their potential threat to the health and well-being of the cigarette smoker. The evidence already presented has dealt largely with those effects of certain components of tobacco smoke as they relate to such problems as myocardial infarction, blood coagulation, and carcinogenesis. What can be done to reduce such hazards as "tar" and nicotine, thus leading to the production of a less harmful cigarette, has been discussed.

This afternoon's workshop seems to me to be a variation on the general theme, being in the nature of a movement written in a minor key. It has dealt with certain components in tobacco smoke, *e.g.*, nicotine, whose deleterious properties have not been experimentally and clinically established, but which are nevertheless under various degrees of suspicion. Therefore, these components must be examined in the process of writing the score for the orchestration of Dr. Wynder's symphony, entitled *Toward a Less Harmful Cigarette.*

Carbon monoxide (CO) is one of these components of tobacco smoke that has long been suspected of being harmful and, hence, has received much study over the years.

The problem of CO as a harmful constituent of tobacco smoke raises two questions:

1. Does the amount of CO in the blood differ between the smoker and nonsmoker?
2. If more CO is present in the blood of the smoker, does it produce either functional or structural pathological changes? Are such changes demonstrable by symptomatic, clinical, or laboratory evidence, and can they therefore be assumed to be detrimental to the health or well-being of the smoker as is true in the case of other components of tobacco smoke?

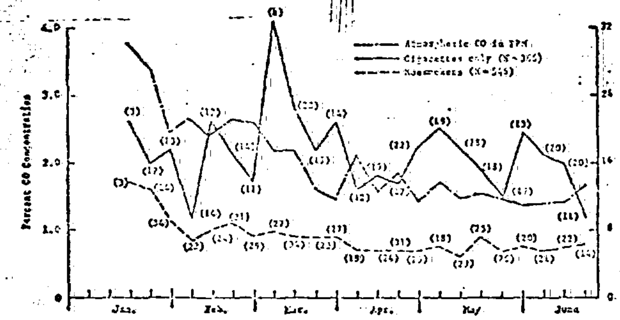
There is abundant evidence in the literature to answer unequivocally the question of the difference between the CO blood level concentration in the smoker and nonsmoker. The article by Larson *et al.* (*1*) is replete with references covering studies over the past 50 years of CO blood levels in smokers and nonsmokers under various conditions, as well as the effect of various quantity levels of smoking on the CO blood level.

Numerous studies on the normal blood level of CO in the nonsmoker show ranges from 0.5-2.5%. In our study, we used 1% as the normal level.

1005051220

Commentary (24) Curphey, Cont.

The data to be presented on the amount of CO in the blood of smokers are a good example of serendipity. Originally our study was aimed at determining whether there was any correlation between the postmortem CO blood levels of individuals handled by the Los Angeles County Medical Examiner's Office and the CO level of the ambient air at the time of death. We were not considering the cause or mode of death, but were looking for a way to use the CO blood level as a daily indicator of air pollution in the Los Angeles basin (text-fig. 1).




TEXT-FIGURE 1.—Distribution median of CO in blood of cigarette-only smokers and nonsmokers.

After analyzing our data, we observed a significant association, which, however, was not noted for every location of the monitoring station. Goldsmith *et al.* (2) who had studied the blood CO levels of longshoremen in San Francisco in relation to their smoking habits suggested that the collected data be used to study the smoking habits of this postmortem population.

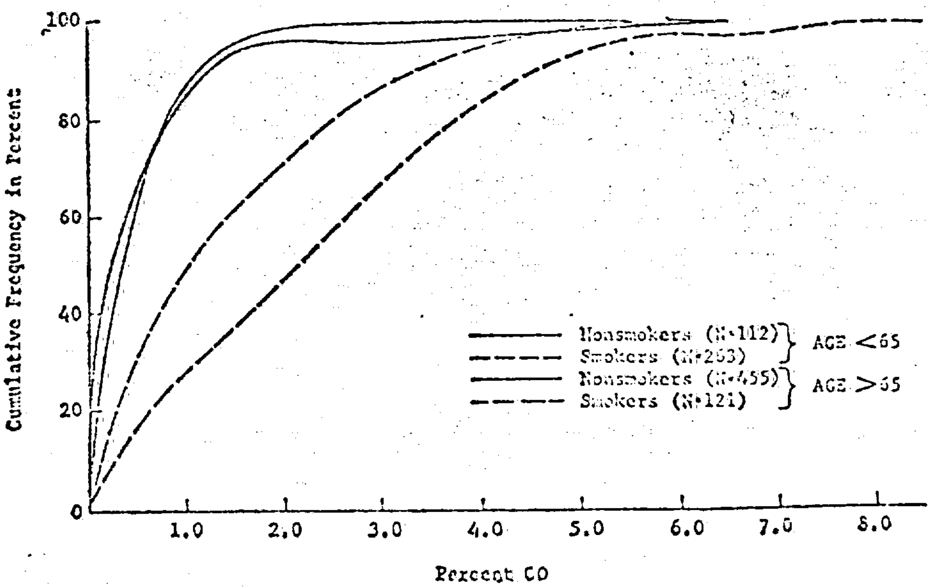
From November 1–June 30, 1961, 2,207 cases were surveyed, and the data were correlated with 1) the CO concentration of the ambient air at certain monitoring stations in Los Angeles and 2) the smoking habits of the study group (3). To determine the smoking habits of the group, a questionnaire was mailed to the next of kin, when known, or to a known informant. This reduced the group to a total of 1,378 persons, from whom we received usable smoking histories for 1,078 persons.

The 1,078 persons were divided into two groups: 1) nonsmokers (including ex-smokers and persons who never smoked), and 2) smokers. These two groups were further subdivided into (*a*) those under age 65 and (*b*) those over age 65. The blood CO levels in the entire group ranged from 0–11.6%. Over 80% of the nonsmokers, regardless of age, fell in the 1% or less CO level. A blood CO level of 5%, regardless of smoking habit, was considered abnormally high.

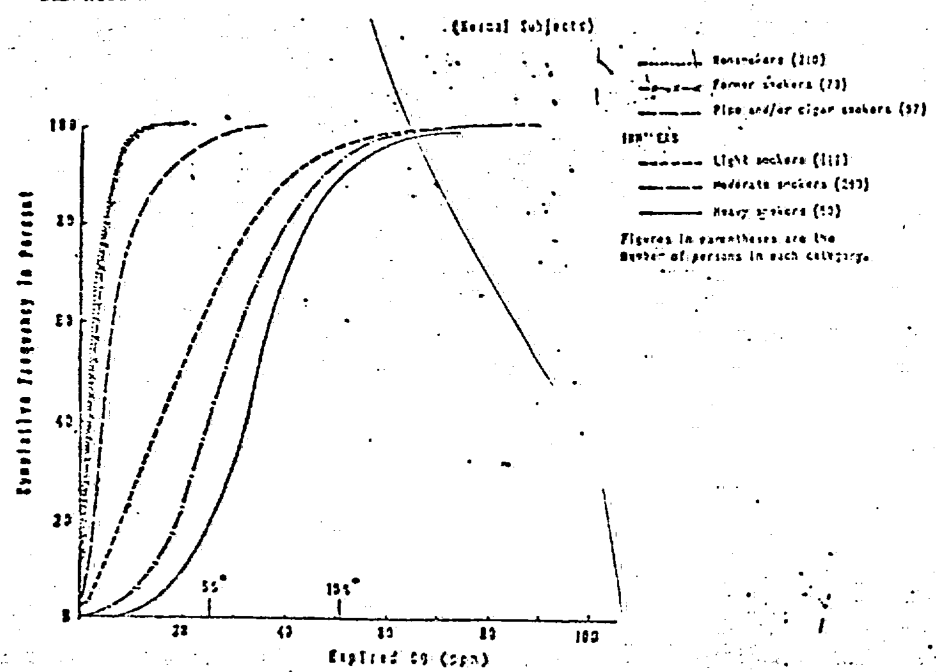
Forty-six persons had values of 5% and all of these were smokers, except 3 who were ex-smokers. Only 7 of the 46 persons were age 65 or over; in other words, 85% of the persons were in the younger age group. Furthermore, with the use of 1% CO as the normal blood level for nonsmokers, 62% of the nonsmokers had less than this level, whereas only 22% of the smokers had values this low (text-fig. 2). Also, the smokers tended to have a much greater frequency at the extreme values of more than 4%. Moreover, smokers over 65 years old had almost twice as high a percentage value under 1% as the smokers under 65 years (text-fig. 2). The interpretation of this finding offers room for speculation, with one possibility being that older smokers might smoke less than their younger counterparts.

Another interesting fact gleaned from a study of the observed median CO values is that the values of male nonsmokers were greater than those of female nonsmokers by a factor of nearly 2. On the other hand, for smokers, the distribution by sex did not show consistent differences.

That there is a direct correlation between the height of the CO blood level and the number of cigarettes smoked is a well-established fact, as demonstrated by Goldsmith (2) in his study of a group of San Francisco longshoremen (text-fig. 3). This is seen in the graph of percentage cumulative frequency of expired CO measured in ppm as related to the smoking habits of his study group.




TEXT-FIGURE 2.—Percentage cumulative frequency and percentage of blood CO in smokers and nonsmokers.



TEXT-FIGURE 3.—Distribution of expired CO in longshoremen, by smoking pattern: ILWU study, 1961. *Percent carboxyhemoglobin concentration based on regression: COHb% = 0.21 + 0.19 X (CO ppm).

Commentary (24) Curphey, Cont.

The graphs of Goldsmith's cases of live persons and of our cases show very good correlation in the CO expressed in ppm of expired air with that obtained from a study of postmortem blood expressed in percentage terms of carboxyhemoglobin concentration.

Goldsmith did not correlate the CO blood levels with the general health of his subjects; and obviously in our series, we were denied that opportunity, since the deaths we studied included those from natural causes due to disease and also homicidal, suicidal, and accidental deaths. In point of fact neither of these studies answers the question "Is smoking dangerous to health?"

Fortunately, there is good evidence available which bridges this gap, namely, the study made by Sievers *et al.* (4) of the effect of exposure to known concentrations of CO on a group of 156 police traffic officers, between 32 and 51 years old, who were assigned to duty in the Holland Tunnel for a period of 13 years. These officers were exposed to an average of 70 ppm of CO, which is equivalent to 10% (COHb saturation), with brief exposures up to 200–300 ppm at times and with the heaviest level for a 24-hour period of 86 ppm (14% COHb). Infrequently, the CO level exceeded 200 ppm (32% COHb) and rarely rose as high as 300 ppm (40% COHb) for a few minutes at a time.

This study on police traffic officers is particularly valuable for the purpose of this workshop, for it demonstrated that these men showed no evidence of injury to their health, as determined by serial physical examinations, blood and urine studies, EKG tracings, blood pressure readings, and neurological examinations. In this latter connection, an excellent test for judging the integrity of the nervous system was the pistol marksmanship record of these officers. The Port Authority pistol team was composed of 7 officers, 6 of whom had tunnel duty, and the team consistently finished in first or second place in formal competition with pistol teams from other police organizations for 7 consecutive years.

Even more pertinent to our charge at this time is the study of the smoking habits of the officers in relation to their blood CO levels. Variation in the entire group ranged from 0.5–18.1% saturation, the highest values being obtained in those who smoked and were stationed on the upgrade section of the tunnel and who were exposed to atmospheric CO readings slightly above 100 ppm (16% COHb saturation) for a 2-hour period in contrast to the average daily value of 70 ppm (10% COHb saturation).

What appears to be the most significant observation in this study of traffic officers in the Holland Tunnel is that the blood CO levels of nonsmokers in the tunnel on the average exceeded those of smokers in an environment free from any occupational exposure to CO. Since these men remained healthy after being consistently exposed for 13 years to CO levels appreciably higher than those found in tobacco smoke, the conclusion then is inescapable that smokers with CO levels that lie well within these same ranges are similarly unaffected by CO.

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(3) CURPHEY, T. J., HOOD, L. P. L., and PERKINS, N. M.: Carboxyhemoglobin in relation to air pollution and smoking: Postmortem studies. Arch Environ Health (Chicago) 10: 179–185, 1965.

(4) SIEVERS, R. F., EDWARDS, T. I., MURRAY, A. L., and SCHRENK, H. H.: Effect of exposure to known concentrations of carbon monoxide: Study of traffic officers stationed at the Holland Tunnel for 13 years. JAMA 118: 585–588, 1942.

1005051223

(25) DINMAN B D : Carbon monoxide and cigarette smoking. JAMA 212: 1785, 1970.

Although the community is concerned with carbon monoxide body burdens arising from ambient concentrations of this gas, it ignores almost totally the most significant source of carbon monoxide intake—the cigarette. This is paradoxical, since the air of our cities rarely contains more than 30 parts of carbon monoxide per million parts of air (ie, 30 ppm); cigarette smoke streams have been reported to contain from 400 to 40,000 ppm carbon monoxide!

The body itself manufactures carbon monoxide in the course of the breakdown of hemoglobin to the extent of about 1 teaspoonful per day. This small amount of carbon monoxide converts about 0.8% of hemoglobin to inactive carboxyhemoglobin. By contrast, the light smoker converts about 3% of his hemoglobin while the heavy smoker inactivates approximately 8% of this blood pigment. Pipe and cigar smokers rarely achieve such loadings. The body has "learned" to adapt to the small amount of self-produced carbon monoxide over the course of evolution. However, the body burden arising from cigarette smoking probably extends beyond the limit of ready accommodation.

What is the significance of such cigarette-caused carbon monoxide body burdens? It is quite clear that visual acuity at low levels of light intensity is impaired with carbon monoxide loadings in the middle of that range of carboxyhemoglobin levels seen among cigarette smokers. Less clear at this time is the effect of carbon monoxide per se upon cardiac function. However, among patients with heart disease whose ability to accommodate is compromised, at levels of 7% to 9% carboxyhemoglobin, there is deterioration in several cardiac-function indices. On the basis of animal experimental data, it appears that long-term carbon monoxide exposures with about 12% carboxyhemoglobin loading are associated with increased deposition of cholesterol in blood vessels. On the basis

Commentary (25) Dinman, Cont.

of epidemiological data, there are some suggestions that this might also apply to humans. In addition, research in mountainous areas suggests that the carbon monoxide loading stemming from cigarette smoking contributes significantly to the development of chronic mountain sickness.

(a) The level of 40, 000 ppm carbon monoxide represents pure cigarette smoke which a smoker does not inhale continuously. The concentration of carbon monoxide in the expired air of a heavy smoker is 16.4 ppm and in that of a light smoker 7.7 ppm (see page 19).

(b) The carboxyhemoglobin levels of 3% as estimated for a light smoker and 8% for a heavy smoker are not supported by the available results of investigations. Balbo et al (1966) reported a mean level of 2.8% for 7 smokers consuming 30 cigarettes daily. Rouch et al (1971) recorded a mean level of 4.25% for 15 smokers using more than 10 cigarettes daily (see page 15).

(c) The investigation quoted refers probably to Aronow et al (1971), who noted a reduction in exercise tolerance when patients with angina pectoris smoked low-nicotine cigarettes. The carboxyhemoglobin blood level is elevated to 7.79% but a cause-and-effect relationship has not been demonstrated (see page 62).

(d) The cited work on cholesterol deposition involves rabbits fed with cholesterol in the diet. In dogs, chronically exposed to 100 ppm carbon monoxide, De Bias et al (1972) failed to exaggerate the signs of myocardial ischemia. There is no experimental support for the statement that a blood level of 10% carboxyhemoglobin is harmful to the ischemic heart (see page 62).

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Commentary (35) Rose, Cont.

When cardiac function is normal there is a significant margin of safety even though the CO intoxication is of long duration. A variety of electrocardiographic aberrations have been observed following CO poisoning, but typically there is a low-voltage pattern.[33] Recovery is apparently rapid following the restoration of oxygen and there is a reversion to a "normal" electrocardiogram; however, enzyme studies may show alterations indicating ischemic heart damage.[32] Epidemiologic studies of cigarette smokers indicate that the death rate from coronary heart disease is considerably higher for smokers than for nonsmokers,[34] and in patients with heart disease there is deterioration of cardiac-function indices at blood levels of seven to nine per cent COHb.[35]

(c) The cited reference for the last sentence is by Dinman (1970), an editorial that is commented upon elsewhere in this report (see page 160).

1005051237

(27) GIEL B G : Air pollution and your lungs. Public Health News 46: 246-53, 1965.

*FACTS ABOUT SPECIFIC AIR POLLUTANTS*

*Carbon Monoxide-*

Carbon monoxide is well known to all of us. Yet many smokers are unaware that approximately seven to eight percent of their hemoglobin may be bound as carboxyhemoglobin. If in the mean time, such an individual should develop vascular insufficiency to vital organs, and then be forced to breath ambient air containing 30 ppm of CO for four to six hours or gotten into an atmosphere where he would be exposed to 120 ppm CO for one hour, he would bind an additional five percent of his hemoglobin and could suffer tragic results.

The figure of 7% to 8% carboxyhemoglobin among smokers is an over-estimation. A review of the literature shows an overall mean of 3.76% for 2,054 smokers 4 to 12 hours after smoking, and a peak level of 5.26% after smoking (see pages 12 to 14 and 20 to 21).

1005051227

(28) GOLDSMITH J R : Carbon monoxide and coronary heart disease. Ann Int Med 71: 199-201, 1969.

A list of future investigations relating to carbon monoxide is included in this Editorial.

The completed jigsaw puzzle may give a clear picture showing that the role of smoking in atherosclerotic diseases is mediated in part by carbon monoxide through such mechanisms as those in the preceding paragraph. Missing pieces are needed: [1] the effects of carbon monoxide exposure with and without vasoactive agents on production of anginal symptoms with exercise; [2] prognostic importance of carboxyhemoglobin levels over both short and long periods of time in cardiovascular diseases; [3] mechanisms and significance of altered hemoglobin binding of oxygen with age, smoking, and other factors; and [4] the possibility of prevention of cardiovascular effects of cigarette smoking when such smoking does not lead to carbon monoxide absorption.

1005051228

(29) GOLDSMITH J R : Carbon monoxide and coronary heart disease: Compelling evidence in angina pectoris. Ann Int Med 77: 808-10, 1972.

This Editorial is devoted largely to the investigations of Aronow. The 2 paragraphs reproduced herewith contain suggestions for future investigations which have not been discussed elsewhere in this review.

We still lack decisive epidemiologic evidence that there is a risk of more rapid development of coronary heart disease in cigarette smokers with high carbon-monoxide uptake, compared with those of the same age and smoking habits but with low carbon-monoxide uptake. We do, however, have convincing evidence that the death rates from coronary heart disease are higher in cigarette smokers than in nonsmokers (6). The 1972 Surgeon General's smoking and health report says, "Experimental and epidemiological investigations implicate the elevation of carboxyhemoglobin levels in smokers as a contributor to the development of CHD and arteriosclerotic peripheral vascular disease." If one estimates the number of excess deaths caused by arteriosclerotic heart disease in smokers in comparison with deaths of people of the same age and sex who are nonsmokers, the potential for prevention is vast. Of the approximately 580 000 deaths in the U.S. caused by arteriosclerotic heart disease, cigarette smoking makes the greatest proportionate contribution to the deaths of those under 60 years old, doubling the mortality ratios in several studies. If we can substantially reduce this toll of deaths and of associated disability by reducing carbon monoxide exposure, it would be a massive public health achievement. We are challenged to develop an alteration in cigarette-smoking behavior that does not permit an increase in carboxyhemoglobin to occur.

It is conceivable that with a cigarette that has a catalytic filter or in which the combustion processes are altered there would be less uptake of carbon monoxide by the smoker. Possibly an alteration in the type of tobacco used would have such effects. Difference in tobacco type is credited with the differential effect of smoking cigars or pipes. Smoking these produces relatively little increase in carboxyhemoglobin compared with that from cigarettes. Although much attention is given to cigarettes that are low in tar and nicotine, practically no attention has so far been given to the public health importance of cigarette smoking that produces a low output of carbon monoxide. Such attention is urgently indicated by the evidence that even small increases in carboxyhemoglobin, as we used to think of them, can decrease the work capacity of persons with angina pectoris.

1005051229

(30) GOLDSTEIN R E and EPSTEIN S E : Medical management of patients with angina pectoris. Prog Cardiovas Dis 14: 360-98, 1972.

*Cigarette Smoking*

Patients with angina who smoke a single cigarette before exercise experience significant decreases in the duration of exercise required to precipitate ischemic pain.[31] The decreased exercise capacity after cigarette smoking is associated with a greater heart rate and blood pressure both at rest and after equal amounts of exercise. Since the pressure-rate product was the same at angina before and after smoking, Aronow and Kaplan concluded that smoking increased $MVO_2$ during exercise, thus precipitating ischemic pain sooner without appreciably altering myocardial oxygen delivery. These authors attributed the alteration in circulatory response to exercise to ganglionic stimulation by nicotine, although subsequent studies[32] using low-nicotine cigarettes yielded the same results as those using ordinary cigarettes. Cigarette smoking might also impair myocardial oxygen delivery in some individuals by converting hemoglobin to carboxyhemoglobin, a change which impairs or destroys the ability of hemoglobin to convey oxygen to tissues. Up to 15% conversion to carboxyhemoglobin can result from heavy smoking.[33]

The last sentence quotes Ayres et al, which is actually an abstract. The statement that heavy smoking can produce a blood level of 15% carboxyhemoglobin is not based on any experimental observations.

**Carboxyhemoglobin (COHB) and the Access to Oxygen: An Example of Human Counter-Evolution**

STEPHEN M. AYRES, MD, FACC; STANLEY GIANNELLI, Jr., MD, FACC; HILTRUD MUELLER, MD, New York, New York

Cigarette smoking and exposure to community air pollution produce COHB saturations between 3 and 15% and decrease both oxygen capacity and the unloading tension of circulating hemoglobin. An individual with 15% COHB has regressed to a hemoglobin which is functionally intermediate between that of an elephant and a newborn goat.

Acute studies performed in 26 subjects demonstrated that elevation of COHB levels to an average of 7.95% increased cardiac output from 5.01 to 5.56 liters/min, increased minute ventilation from 6.86 to 8.64 liters/min, and decreased arterial and mixed venous oxygen tension from 81 and 39 to 76 and 31 mm Hg, respectively. Myocardial studies performed by coronary sinus catheterization demonstrated that similar elevations of COHB increased coronary blood flow, decreased coronary artery-coronary sinus oxygen content and decreased coronary sinus oxygen tension. The changes were most marked in patients with coronary artery disease or chronic emphysema, lactate extraction decreasing in 10 of 15 patients. The possibility of adaptation was studied by achieving similar COHB concentrations with both a low and high concentration of carbon monoxide. Hemodynamic changes appeared more marked with administration of the high concentration even though COHB was the same.

These studies suggest that COHB concentrations between 5 and 10% may produce abnormal myocardial function in certain individuals. The well-known deleterious effect of cigarette smoking on the heart may be explained by the interaction of COHB and nicotine, the latter increasing cardiac work and the former decreasing oxygen availability.

1005051230

(31) LINDQUIST V A Y : Carbon monoxide: Its relationship to air pollution and cigarette smoking. Public Health London 86: 20-6, 1970.

> Cigars and pipe tobacco produce more CO than cigarettes, but cigarette smokers tend to have higher levels of COHb because they usually inhale. The gas phase of cigarette smoke contains 1-5% CO (Osborne *et al.* 1965; Bokhoven & Niessen, 1961) and the concentrations tend to be highest as the cigarette is smoked down toward the butt-end. Continuous exposure to such ambient concentrations would normally render a man unconscious in a few minutes. However, inhalation of cigarette smoke is both transient and intermittent and the gas is diluted with atmospheric air so that a single cigarette would not be expected to produce an immediate rise in COHb of more than 3%. During the course of a day, those who smoke heavily and inhale usually have mean COHb concentrations in excess of 4% and may even exceed 10% (Ayres *et al.*, 1965; Goldsmith & Landaw, 1968).

(a) This is a more accurate summary of carboxyhemoglobin levels in cigarette smokers.

### Myocardial Oxygenation

> Those organs with high oxygen consumption leave little "reserve" in the blood supplying them and therefore rely more on increased perfusion to meet any extra demand for oxygen. The myocardium is a typical example. A combination of high oxygen demand, poor perfusion, lowered oxygen capacity and impaired oxygen uncoupling from the blood will obviously prejudice tissue respiration. This was classically demonstrated by Ayres *et al.* (1969, 1970). In a group of noncoronary disease patients undergoing cardiac catheterization raising the COHb level to 9·0% produced a significant increase in coronary perfusion. Despite this, however, the oxygen tension of coronary sinus blood, and presumably of the myocardium itself, dropped slightly. After raising the COHb to a similar degree in a group with established coronary disease, the increase in perfusion was less marked and there was definite reversal of lactate and pyruvate extraction in addition to a drop in oxygen extraction. This indicated significant myocardial hypoxia.

(b) The experiments of Ayres et al (1969, 1970), consisting of inhalation of carbon monoxide causing blood levels of 9.0% are probably in error. This is discussed elsewhere in the present commentary (see page 148).

(32) NAHUM L H: Smoking and thrombosis. Conn Med 29: 853-4, 1965.

The next problem is to determine by what mechanism does smoking accelerate thrombosis. Employing the method of multiple working hypotheses, a number of possibilities immediately present themselves. One is that smoking produces an increase in carbon monoxide hemoglobin up to 15-20 per cent which somehow promotes thrombosis. Another is that nicotine absorption itself sets into operation the thrombotic process. A third possibility is the well known effect of nicotine in liberating increased amounts of epinephrine which may be the real culprit in accelerating thrombosis. A fourth possibility is that smoke irritation in the bronchial mucosa liberates into the blood stream a thrombus inducing agent. Perhaps there are other possibilities as yet unidentified.

That cigarette smoking produces an increase in carboxyhemoglobin of up to 15% to 20% is a rarity. In a review of the literature, it was found that out of 30 investigations only Meigs (1948) reported a mean level of 16.2% for a group of 6 habitual smokers. The overall mean level for 2,054 subjects reported in 29 investigations was 3.76% (see page 12).

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(33) NAHUM L H : Toxic products in cigarette smoke: pleasure or poison.
Conn Med 32: 154-5, 1968.

Okay, well let's see what it is that the cigarette smoker inhales. Most people when they consider air pollution think of the automobile, the smoke-stack or the trash burners. It's time then to point to a most damaging source of air pollution, the cigarette. One of the toxic products of the automobile exhaust is carbon monoxide (CO). Exposure for one hour to a concentration of this gas of 120 parts per million causes inactivation of about 5 per cent of the body hemoglobin by forming CO hemoglobin. Concentrations of CO as high as 100 ppm. often occur in garages, in tunnels, and behind automobiles. Such concentrations are tiny in comparison with those (42,000 ppm.) found in cigarette smoke!

The smoker survives because most of the time he breathes air not so heavily polluted. Nevertheless the smoker can carry 15 to 20 per cent CO hemoglobin for hours and seriously reduce the oxygen supply to already compromised areas in the brain, heart and elswhere whose arteries are narrowed by atherosclerotic disease. Furthermore, in a poorly ventilated smoke-filled room concentrations of CO can easily reach several hundred parts per million thus exposing smokers and non-smokers present to a toxic hazard The headache and fatigue that those exposed experience after a time in such an atmosphere is no accident and not psychosomatic.

The concentration of carbon monoxide that a smoker is exposed to continuously is not 42, 000 ppm. This is the concentration of pure cigarette smoke which reaches the lung diluted with atmospheric air. The concentration of carbon monoxide in expired air would be a more reasonable estimation. Ringold et al (1962) have reported the following observations with regard to the latter: heavy smokers had a concentration of 16.4 ppm, light smokers 7.7 ppm and non-smokers 0.8 ppm (see page 19).

(34) NAHUM L H: The effects of carbon monoxide on human health. Conn Med 33: 90-2, 1969.

> CO occurs in high concentration in cigarette smoke greater than 2 per cent, this means 20,000 ppm. although an estimate of the average concentration in smoke is much less—400 ppm. In a population of longshoremen smoking produced 6 per cent of COHb. When it comes to occupational exposure 12-14 per cent of employed persons had occupations in which there is a likelihood of exposure. Various forms of indoor combustion may emit CO and a number of deaths each year are due to poisoning from this source. Gas fired baseboard heaters were incriminated by Michigan State Department of Public Health. Open fires and charcoal braziers produce substantial amounts of CO.

(a) Blood levels of habitual smokers have been reported by 11 groups of investigators. The overall peak after smoking was 5.26% (see page 20). The blood levels 4 to 12 hours after smoking have been reported by 30 groups of investigators with an overall mean of 3.76%. The smoker throughout 24 hours sustains a level between 3.76% and 5.26% (see page 12).

> Grut[2] alleged that 46 per cent of 721 drivers had chronic CO poisoning characterized by fatigue, headache, irritability, dizziness, disturbed sleep and other symptoms. Some subjects had abnormal neurological symptoms. From the epidemiological point of view it is desirable to obtain data which would show whether there are CO associated increases in such relatively frequent events as motor vehicle accidents or in fatality rates with myocardial infarction to confirm the data from the Los Angeles Hospitals where an association of CO and case fatality rates in 3,080 patients with myocardial infarction was observed. The central nervous system effects are definitely due to anoxia. The mechanism of myocardial effects probably are similarly produced. Lindenberg[3] did obtain significant electrocardiographic changes on exposing dogs for six weeks to 50 ppm. CO. They also showed dilatation of the right ventricle, scarring of heart muscle and fatty degeneration. A very important question for epidemiologists to study is whether exposure to low concentrations of CO have a role in the development of human heart disease. Inferring from results of acute toxicologic and experimental studies, we can begin to appreciate the abundant data linking cigarette smoking to coronary heart disease. As far as cigarette smoking is concerned we must keep in mind that high levels of COHb. imply also increased respiratory absorption of other ingredients of tobacco smoke.[4]

Commentary (34) Nahum, Cont.

It is safe to say that exposure to CO. is widespread, that the smoker who inhales 6 per cent CO. is developing a blood concentration which is a serious threat to the health in persons with underlying cardiovascular disease. It is also true that community air pollution may produce COHb. in nonsmokers similar to that observed in smokers. Even low and commonly occurring CO. exposures may impair performance of complex psychomotor tasks. Finally that CO. has a role in motor vehicle accidents, is supported by data of high COHb. in many drivers involved in accidents.

L.H.N.

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1. Goldsmith, J. R. and Landow, S. A.: Carbon monoxide and human health. Science, 162: 1352, December 20, 1968.
2. Grut, A.: Chronic carbon monoxide poisoning. (Munksgaard) Copenhagen, 1949. p. 48.
3. Lindenberg, R., Levy, D., Preziosi, T. and Christensen, M.: paper presented at a meeting of the American Industrial Hygiene Association, Washington, D.C., 1962.
4. Nahum, L. H.: Toxic products in cigarette smoke: pleasure or poison. Conn. Med., 32: 154, March, 1968.

(b) Each statement in this paragraph can be challenged by work of other investigators. For instance, at a meeting Lindenberg et al presented the electrocardiographic changes on exposing dogs for 6 weeks to 50 ppm carbon monoxide. De Bias et al (1972) published the results of their investigations indicating that exposure of dogs to 100 ppm carbon monoxide for 14 weeks does not influence the heart that has been previously infarcted (see page 62).

(35) ROSE E F and ROSE M : Carbon monoxide: A challenge to the physician. Clin Med 78: 12-21, 1971.

(a) The amount of CO in cigarette smoke varies between 1 and 2.5 per cent by volume,[4] and can create discomfort not only for the addict but also for others in the environment. For the average smoker, the concentration of CO reaching the alveoli is about 0.04 per cent (400 ppm). The importance of cigarette-produced CO is amply demonstrated by samplings from fleet submarines submerged for extended periods. In 30 hours, concentrations may reach 0.01 per cent (100 ppm),[5] with cigarette smoke accounting for 75 to 80 per cent of the CO production.[6] This exceeds the allowable maximum concentrations recommended by the American Conference of Governmental Industrial Hygienists, which states that CO concentrations in the atmosphere should be kept below 50 ppm.[7]

(a) The concentration of carbon monoxide reaching the alveoli is not 400 ppm for the average smoker. Jongbloed (1939) noted the highest level of 31.5 ppm after a subject finished smoking a 4th cigarette (see page 19).

(b) Because individuals who smoke from 20 to 30 cigarettes daily have a COHb level ranging from three to 10 per cent,[16] there is a widespread mistaken idea that smokers are more susceptible to environmental CO than are nonsmokers. CO from cigarettes and CO in the ambient air are not additive in their biologic effects. CO is absorbed into the bloodstream only when the pressure of CO in the ambient air exceeds that in the pulmonary capillary blood. Thus, persons with COHb levels of five per cent as a result of smoking do not absorb further CO unless the environmental CO concentrations exceed 0.003 to 0.004 per cent.

(b) The cited reference 16 is Barach et al (1941). Although the range is 3% to 10%, the mean value is 5.7% for the carboxyhemoglobin level. Other groups of investigators reported mean values of 4.3 and 4.85% (see page 21).

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Commentary (35) Rose, Cont.

When cardiac function is normal there is a significant margin of safety even though the CO intoxication is of long duration. A variety of electrocardiographic aberrations have been observed following CO poisoning, but typically there is a low-voltage pattern.[33] Recovery is apparently rapid following the restoration of oxygen and there is a reversion to a "normal" electrocardiogram; however, enzyme studies may show alterations indicating ischemic heart damage.[32] Epidemiologic studies of cigarette smokers indicate that the death rate from coronary heart disease is considerably higher for smokers than for nonsmokers,[34] and in patients with heart disease there is deterioration of cardiac-function indices at blood levels of seven to nine per cent COHb.[35]

(c) The cited reference for the last sentence is by Dinman (1970), an editorial that is commented upon elsewhere in this report (see page 160).

(36) SELTZER C C : The effect of cigarette smoking on coronary heart disease. Arch Environ Health 20: 418-23, 1970.

This article reviews the effect of cigarette smoking on coronary heart disease. Seltzer discusses the shortcomings of interpretations appearing in the Surgeon General's report. The question as to the role of carbon monoxide in cigarette smoke is discussed. It should be noted that the work of Ayres quoted in the article has been commented upon elsewhere (see page 148).

6. Does the carbon monoxide constituent of cigarette smoke result in or contribute to increased myocardial infarction or sudden death either in normal individuals or in persons with already impaired coronary circulation due to CHD?

Studies have shown that the carbon monoxide constituent of cigarette smoke does effect increases (2% to 10%) in the levels of carboxyhemoglobin (COHb) saturation when heavy cigarette smokers and nonsmokers were compared, with the consequent displacement of oxyhemoglobin. In addition, carbon monoxide effects a shift to the left of the oxygen-hemoglobin dissociation curve, which may result in a decreased release of oxygen at the tissue level.[23]

On the whole, experimental and clinical investigations bearing on this question are few. The most salient work in this area has been performed by Ayres and associates.[24] In 26 human subjects before and after carbon monoxide inhalation, these investigators found no significant change in oxygen tension. In another experiment, after exposure to carbon monoxide, coronary blood flow increased significantly in seven non-CHD patients but not in four patients with arteriographically proven CHD. In the patients with CHD, myocardial lactate and pyruvate extraction decreased or shifted to actual production, suggesting anaerobic metabolism.

If carbon monoxide does in fact appreciably decrease oxygen extraction at the myocardial level, the matter of oxygen consumption may hinge on the extent of increase in coronary blood flow in normal persons, while in persons with diseased coronary arteries, the increase in blood flow is slight or absent. Hence, it may be a question of the ultimate balance of these opposing forces. In normal persons, there is the presumption that the increased coronary blood flow more than matches the presumed decrease in oxygen extraction. Whether or not this fails to occur in patients with obvious CHD, to such an extent as to "trigger" a coronary event is as yet unknown and much work remains to be done in this area.

1005051238

(9) ANON: Carbon monoxide poisoning - a timely warning. New England J Med 278: 849-50, 1968.

> The cigarette is another producer of carbon monoxide. Heavy cigarette smokers may have as much as 10 per cent carbon monoxide hemoglobin in their blood. Such levels may not be sufficient to cause impairment at sea level but will be enough to produce changes at altitudes of 8000 to 10,000 feet. A recent article has demonstrated behavioral impairment associated with small doses of carbon monoxide[3] – levels of exposure in the range accepted as tolerable in industry. The results indicate that impairment of cerebral function can occur at extremely low levels (50 to 250 ppm) during exposures of half an hour to two and a half hours. Further support for central-nervous-system effects comes from the observation that low levels of carbon monoxide hemoglobin can significantly raise the threshold of light sensitivity of the eye.[4]

That heavy cigarette smoking may cause as much as 10% carboxyhemoglobin in the blood is rare. Barach et al (1941) measured the peak levels in the blood of 18 subjects who smoked 20 cigarettes daily and noted a mean level of 5.7%, with a range of 2.2% to 12.3%. Fabre et al (1951), in a group of 5 subjects smoking 24 cigarettes, reported a mean level of 4.85%, which represented an increase of 2.7% over the level prior to smoking (see page 21).

Additional Bibliography List, No. 1

ANALYSIS OF CARBOXYHEMOGLOBIN IN THE BLOOD


Reprint

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## I. INTRODUCTORY REMARKS

In recent years there has been increasing concern as to the harmful effects of carbon monoxide released as an air pollutant. The importance of cigarette smoking as a source of carbon monoxide has been recently stressed. This review is an attempt to clarify the role of carbon monoxide in cigarette smoking. The relationship will be analyzed in terms of carboxyhemoglobin blood levels and their influence on the respiratory, circulatory, nervous, renal, reproductive, endocrine and musculoskeletal systems.

At the outset it is pertinent to summarize the present state of knowledge relating to carbon monoxide in general and to carbon monoxide in cigarette smoke in particular. The information is summarized in the following publications:

a. The toxicity of carbon monoxide has been reviewed by Sayers and Davenport (1930), Killick (1940), Lilienthal (1950), Root (1962) and Theodore et al. (1971). These review articles have appeared at intervals of a decade and do not include the cigarette smoke as a source of carbon monoxide.

b. The importance of carbon monoxide as an air pollutant has been reviewed by Goldsmith (1964), Kaye (1965), Finck (1966), Giever (1967), Goldsmith and Landaw (1968), Beard (1969), Leclerq and Proteau (1970), Casarett (1971) and Jech (1972). These reviews appearing at yearly intervals emphasize the origin of carbon monoxide poisoning from sources other than cigarette smoking.

(26) DOYLE J T: Smoking and myocardial infarction. Circulation 39 & 40: Suppl 4: 136-43, 1969.

This review contains a paragraph on the role of carbon monoxide in pathogenesis of atherosclerosis. The author views the problem in the proper perspective.

/ The manner in which cigarette smoking accelerates atherosclerosis and its complications is, in short, unexplained. It is possible that in some way cigarette smoking damages the arterial intima. Carbon monoxide is the likeliest immediate candidate for such a role. Some presently mysterious interference with the normal mechanism of transport of lipids from the plasma through the vascular tunics to the lymphatics secondary to the inhalation of cigarette smoke is an alternative possibility. in all populations yet scrutinized, the prevalence and incidence of CHD rise with the serum cholesterol concentration.[22] It is, accordingly, a plausible hypothesis that inordinate cigarette smoking may be associated with an increased serum cholesterol concentration. Such a relationship does, indeed, exist, but is unimpressive. Although the serum cholesterol concentration in both men and women is consistently higher in cigarette smokers, the influence of increasing age is substantially greater (figs. 1 and 2).[23] The observation that heavy cigarette smokers have far more atheroma than nonsmokers is, possibly, complemented by Astrup's observation that fat-fed rabbits exposed to high tensions of carbon monoxide exhibit extreme hyperlipidemia and cholesterosis as compared to controls not exposed to carbon monoxide.[2-5, 26] This interesting experimental model has, however, no recognized counterpart in human epidemiological studies. Obesity as a coronary risk factor is not related to cigarette smoking.[2] Lastly, the arterial blood pressure is not associated with cigarette habit.[2]

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## V. CIRCULATORY SYSTEM

The investigation of circulatory effects of carbon monoxide has been more extensive than that of its effects on the respiratory system discussed in the preceding section. There has been increasing concern that chronic exposure to carbon monoxide present in cigarette smoke would lead to diseases of the heart and blood vessels and abnormalities in the composition of the blood. However, the problem has not been solved by direct experimentation relating to the carbon monoxide in cigarette smoke. There are numerous observations regarding the effects of sublethal concentrations of carbon monoxide in man and animals. These are reviewed in the following paragraphs, although they are only remotely related to the small amount of carbon monoxide contained in cigarette smoke.

### V A. Heart Rate

The acceleration of heart rate known to occur during inhalation of cigarette smoke is explained by the nicotine content. The amount of carbon monoxide in the smoke does not influence heart rate, since experiments consisting of administering carbon monoxide alone in amounts even exceeding that produced by cigarettes failed to alter the electrocardiogram.

The electrocardiograms of patients suffering from acute carbon monoxide poisoning or chronic exposure to carbon monoxide show the following alterations: depression of S-T segment (Steinmann, 1937; Störmer, 1938; Wendt, 1941; Graybiel, 1942; Breu, 1943; Patz, 1949; Saracoglu, 1951); sinus arrhythmia (Breu, 1942); premature systole (Parade and Franke, 1939); atrial flutter

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## VI. NERVOUS SYSTEM

### C. Hearing and Auditory Pathways


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